EVALUATION OF PREGABALIN PREMEDICATION ON ATTENUATION OF HEMODYNAMIC RESPONSE TO ENDOTRACHEAL INTUBATION AND ON POSTOPERATIVE FENTANYL REQUIREMENT

Dissertation submitted to
THE TAMILNADU DR. M.G.R.MEDICAL UNIVERSITY

in partial fulfilment for the award of the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

BRANCH – X

INSTITUTE OF ANAESTHESIOLOGY & CRITICAL CARE
MADRAS MEDICAL COLLEGE
CHENNAI- 600 003

APRIL 2013

DECLARATION

I hereby declare that the dissertation entitled **"EVALUATION OF PREGABALIN PREMEDICATION ON ATTENUATION OF HEMODYNAMIC RESPONSE TO ENDOTRACHEAL INTUBATION AND ON POSTOPERATIVE FENTANYL REQUIREMENT "** has been prepared by me, under the Guidance of **Prof.Dr.T.VENKATACHALAM,M.D.,D.A.,** Professor of Anaesthesiology, Institute Of Anaesthesiology and Critical Care, Rajiv Gandhi Govt.General Hospital, Madras Medical College, Chennai, in partial fulfillment of the regulations for the award of the degree of M.D[Anaesthesiology], examination to be held in April 2013.

This study was conducted at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

I have not submitted this dissertation previously to any university for the award of any degree or diploma.

Date :
Place : Chennai **Dr. P. RAMESH KUMAR**

CERTIFICATE

This is to certify that the dissertation entitled, **"EVALUATION OF PREGABALIN PREMEDICATION ON ATTENUATION OF HEMODYNAMIC RESPONSE TO ENDOTRACHEAL INTUBATION AND ON POSTOPERATIVE FENTANYL REQUIREMENT"** submitted by **Dr.P.RAMESH KUMAR**, in partial fulfilment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamilnadu Dr. M.G.R. Medical University, Chennai is a bonafide record of the work done by him, in the INSTITUTE OF ANAESTHESIOLOGY & CRITICAL CARE, Madras Medical College, during the academic year 2010-2013.

DR.M.VASANTHI,M.D.,D.A.,DNB.,
PROFESSOR AND DIRECTOR
INSTITUTE OF ANAESTHESIOLOGY &
CRITICAL CARE
MADRAS MEDICAL COLLEGE
CHENNAI- 600003

DR.V.KANAGASABAI, M.D.,
DEAN
MADRAS MEDICAL COLLEGE
& GOVT.GENERAL HOSPITAL
CHENNAI-600003

ACKNOWLEDGEMENT

I extend my sincere thanks to **PROF. DR.KANAGASABAI, M.D., DEAN,** Madras Medical College, for granting me permission to carry out this study.

I am thankful to our **PROF. DR.M.VASANTHI, MD.,DA.,DNB DIRECTOR AND PROFESSOR,** Institute Of Anaesthesiology and Critical Care, for her constant motivation and support.

I am immensely grateful to **PROF.DR.C.R.KANYAKUMARI M.D.,D.A.,** First Director and Retired Professor, Institute Of Anaesthesiology and Critical Care, for her support and encouragement to choose the study.

I also express my very sincere gratitude to my guide **PROF.DR.T.VENKATACHALAM, M.D,D.A,** Professor of Anaesthesiology, Institute Of Anaesthesiology and Critical Care, Rajiv Gandhi Govt.General Hospital,Madras Medical college, Chennai, who helped me in choosing the subject and guided me at every stage of this study with his timely advise and valuable suggestions.

I am thankful to all my Professors, **PROF. DR. B.KALA, MD.,DA, PROF.DR.ESTHER SUDHARSHINI RAJKUMAR, M.D.,D.A, PROF.DR.SAMUEL PRABHAKAR M.D.,D.A, PROF.DR.GANDHIMATHY, M.D.,D.A,** Institute Of Anaesthesiology and Critical Care, for their guidance and encouragement.

I am very grateful and specially thankful to **Dr G.K.Kumar, MD.,DA** for the constant encouragement he offered me throughout the duration of this work.

I am thankful to all our Assistant Professors , Institute of Anaesthesiology & critical care, without whose immense help and support this work will not have ended successfully.

I thank all other Department professors and postgraduates who have rendered their support and guidance, which helped me in this venture.

I am thankful to the Institutional Ethical Committee for their guidance and approval for this study.

I am thankful to all my colleagues and junior friends for their help in carrying out this dissertation.

I am thankful to the theatre staff, anaesthesia technicians, theatre assistants for their help during the study.

My sincere thanks to our statistician, who played an important role during my study.

I am grateful to my family and friends for their moral support and encouragement.

Last but not the least, I thank all the patients for willingly submitting themselves for this study.

Above all I pay my gratitude to the lord Almighty for blessing me to complete this work.

ABBREVATIONS

HR	-	Heart rate
ECG	-	Electrocardiograph
SAP	-	Systolic blood pressure
DAP	-	Diastolic blood pressure
MAP	-	Mean blood pressure
PCA	-	Patient controlled analgesia
SPO2	-	Oxygen saturation
GABA	-	Gamma amino butric acid
ASA	-	American society of anesthesiologist

CONTENTS

INTRODUCTION

Laryngoscopy and endotracheal intubation is one of the key skills in anesthesiology.

Sir William Maceven, a Scottish surgeon was the first to perform endotracheal intubation in 1880. American otolaryngologist Dr. Chevallier Jackson developed the scientific principles of laryngoscopy and endotracheal intubation. The occurrence of hemodynamic response to laryngoscopy and intubation was evident after the advent of neuro muscular relaxant.

The act of laryngoscopy and intubation elicits reflex tachycardia and hypertension. Though this stress response is transient, it is profound enough to cause undesired effects on cardiovascular system like dysrhythmias, and myocardial ischemia[1]. Hence, this laryngoscopy and intubation induced stress response needs to be attenuated.

The reflex response to instrumentation of airway is sympathetic rather than a vasovagal response. The previous studies which showed increase in serum catecholamine level during laryngoscopy and intubation supports the fact that the reflex response is sympathetic[2]. Blunting of the stress response by beta receptor blockade, further confirms this concept.

The various pharmacological methods to attenuate hemodynamic stress response to laryngoscopy and tracheal intubation are listed below. The efficacy and adverse effects of these techniques varies, with none of the method being superior to another.

- Beta receptor blocking drugs
- Calcium channel blocking drugs
- Topical or parenteral lignocaine
- Opioids like fentanyl or remifentanil
- Vasodilating drugs
- Deepening the level of anesthesia
- Omitting anticholinergic premedication

Gabapentenoid group of drugs:

Gabapentenoid group of drugs includes Gabapentin and Pregabalin. They are structurally related to the inhibitory neurotransmitter gamma amino butryric acid (GABA). These drugs possess anticonvulsant, sedative, anxiolytic, and antihyperalgesic effects. Pregabalin is approved by FDA for use as adjunctive therapy in partial seizure, chronic pain syndromes like diabetic neuropathic pain, and post herpetic neuralgia. Studies have been done regarding potential perioperative use of gabapentenoids.

Pregabalin:

Pregabalin has similar structure and mechanism of action as gabapentin. Recent studies have evaluated the role of Pregabalin premedication on anxiolysis, attenuation of stress response to laryngoscopy and opioid sparing effect. These studies claim favourable response to Pregabalin and absence of significant side effects.

Potential perioperative use of Pregabalin:

Clinical investigations done with Pregabalin premedication have concluded that it produces useful preoperative sedation, anxiolysis, and attenuates pressor response to laryngoscopy and intubation. The exact mechanism by which Pregabalin attenuates laryngoscopic stress response is not known. Blunting the release of excitatory neuro aminoacids, due to blockade of alpha2 delta subunit of neuronal calcium channels could be the possible mechanism[3].

Pregabalin as an adjuvant in acute pain management:

Adjuvants are substances which by themselves are ineffective, but when combined with opioids, they reduce the opioid requirement and thereby its adverse effects. There is heightened interest in the evaluation of Pregabalin as a good adjuvant to opioids.

Surgical pain causes a hyper excitation phenomenon by simulating the pain pathways and this increases the magnitude of post-operative pain with consequent increase in opioid requirement. By blunting this hyper excitation phenomenon, Pregabalin produces an antihyperalgesic effect.

There are several studies which evaluated various doses of gabapentin on attenuation of laryngoscopic stress response and its effect on acute pain management. But there are only limited studies done with pregabalin regarding the same clinical implications.

This study was designed to evaluate the efficacy of single oral dose of 150mg pregabalin given one hour before induction on the attenuation of hemodynamic response to tracheal intubation and the requirement of fentanyl in the early post-operative period and its side effects.

AIM OF THE STUDY

The aim of this study was to evaluate the efficacy and safety of Pregabalin premedication, administered as a single 150 mg oral capsule an hour before surgery on the following features,

1. The potential perioperative benefits.
2. Efficacy of attenuation of hemodynamic stress response to laryngoscopy and intubation.
3. Interference on recovery from general anesthesia.
4. Postoperative patient controlled analgesic (PCA) requirement of Fentanyl over the first 12 hours after surgery.
5. Adverse effects of Pregabalin.

ANATOMY OF UPPER AIRWAY[4]

The upper airway comprises of mouth, nasopharynx, oropharnnx, and larynx. This is the most vulnerable area to obstruction and may get traumatised during laryngoscopy. Pharynx is a fibro muscular tube that extends from the base of the skull to the lower border of cricoid cartilage.

Nerve supply to upper airway:

The sensory nerve supply to the upper airway is derived from the cranial nerves. The mucous membrane of the nose is supplied by ophthalmic division of trigeminal nerve anteriorly and by the maxillary division posteriorly. Soft palate and hard palate are supplied by the palatine branches of trigeminal nerve.

Anterior two-third of tongue gets general sensation from lingual nerve, a branch of mandibular division of trigeminal, and taste sensation from branches of facial nerve. Posterior third of tongue gets general and taste sensation both from glossopharyngeal nerve.

The glossopharyngeal nerve also innervates the roof of pharynx, tonsils, and the under surface of soft palate. The vagus provides sensation below epiglottis. The pharyngeal surface of epiglottis is supplied by glossopharyngeal and the laryngeal surface by the vagus nerve.

The superior laryngeal branch of vagus divides into external and internal laryngeal nerve. The superior laryngeal nerve gives motor branch to the cricothyroid muscle. All other muscles of larynx are supplied by recurrent laryngeal nerve.

The sensory supply of larynx from epiglottis to vocal cords is supplied by internal laryngeal nerve. Sensation below vocal cords and trachea is supplied by the recurrent laryngeal branch of vagus.

PHYSIOLOGY OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND INTUBATION[5]

Hemodynamic response occurs during the act of laryngoscopy and to subsequent tracheal intubation. These responses are transient but profound enough to cause morbidity and mortality. Tachycardia and hypertension response are the common hemodynamic response. These circulatory changes are detrimental in elderly, hypertensive, and ischemic heart disease patients leading on to myocardial infarction or dysrhythmias.

Cardiovascular response

The unpredictable cardiovascular response to upper airway stimulation can be both sympathetically and Para sympathetically mediated. The occurrence of bradycardia in neonates and infants is mediated by increase in vagal tone at the SA node and is virtually a monosynaptic response.

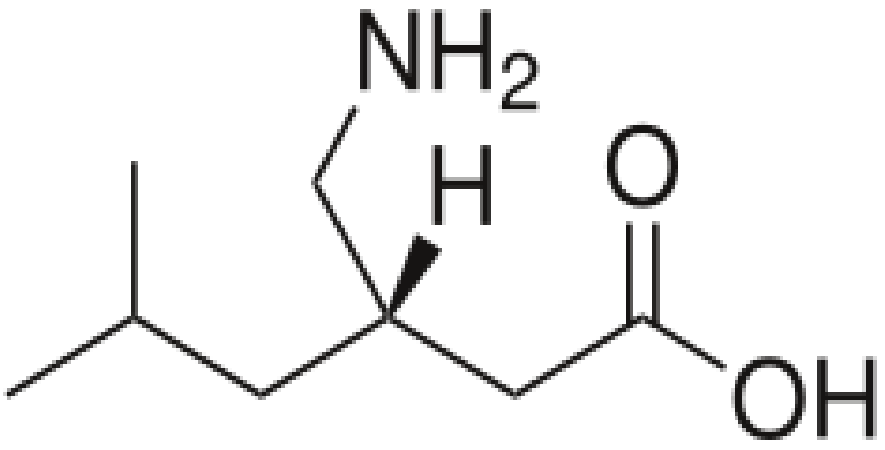
But the more common tachycardia and hypertension response is mediated by discharge from sympathetic efferent through cardioaccelerator fibres and sympathetic chain ganglion.

The afferent impulses from IX to X cranial nerves carried to the sympathetic nervous system via brain stem and spinal cord are polysynaptic in nature. This results in diffuse autonomic response which includes the release of norepinephrine form adrenergic nerves and epinephrine from adrenal medulla. Release of renin from juxta-glomerular apparatus due to activation of renin angiotensin system is also a proposed mechanism.

PHARMACOLOGY OF PREGABALIN[6,7]

Pregabalin belongs to gabapentenoid group of drugs. It possesses chemical structure similar to inhibitory neurotransmitter GABA (gamma amino benzoic acid). Pregabalin has got similar properties like the prototype drug gabapentin.

Fig-1: Chemical structure of Pregabalin



Pregabalin which is chemically S-(+)-3-isobutylgaba (Fig-1), was designed as a lipophilic analogue of GABA (gamma-aminobutyric acid) substituted at the 3-position to facilitate diffusion across blood brain

barrier. 3-isobutylgaba exists in isomeric forms, rendering the drug pharmacologically active enantiomer.

Drug approval[6]

- July 2004–European Commission, granted the pharmaceutical company Pfizer approval for pregabalin, for the treatment of peripheral neuropathy and as an adjunctive therapy for partial seizures in patients with epilepsy.
- December 2004-The Food and Drug Administration (FDA) approved pregabalin, for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and post herpetic neuralgia.
- June 2005-The FDA approved pregabalin for use as an adjuvant in partial seizure treatment.
- March 2006- Pregabalin got approval from European commission, for the treatment of generalised anxiety disorder
- Pregabalin is placed in Schedule V of the controlled substance act, based on the report of euphoria in controlled clinical trials.

Mechanism of action:

Pregabalin is only structurally related to the inhibitory neurotransmitter GABA. It neither acts on GABA receptor, nor mimics it physiologically. The precise mode of action of pregabalin has not been fully elucidated. Pregabalin has got similar pharmacological profile as gabapentin. The main site of action of pregabalin is on the alpha 2 delta subunit of neuronal calcium channels.

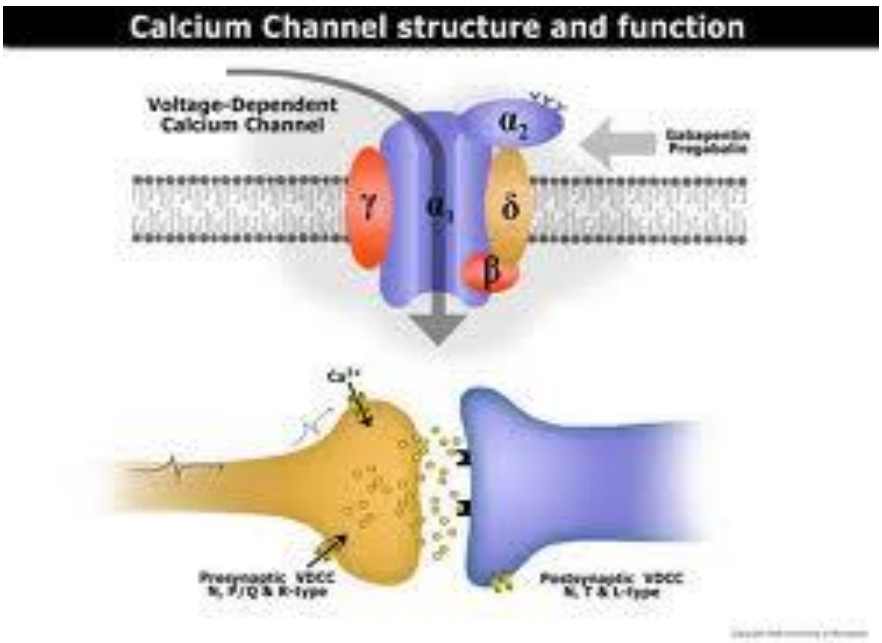
Pregabalin is an alpha 2 delta ligand[7]

Alpha 2 delta is a subunit of presynaptic, voltage-gated calcium channel. The main site of action of pregabalin is this alpha 2 delta subunit of neuronal calcium channels. This binding reduces the depolarisation induced calcium influx at nerve terminals. As a consequence, there is reduction in the release of several excitatory aminoacids, like glutamate, noradrenaline, substance-P, and CGRP. This modulation of neurotransmitter release by pregabalin contributes to its anticonvulsant, anxiolytic, and analgesic property.

Voltage gated calcium channels are divided into six types P, Q, N, L, R, and T-type channels. N-type calcium channels are involved in pain sensitization phenomenon in response to noxious stimuli. Calcium channel blockers like nifedipine binds to L-type channels, whereas

pregabalin binds to N-type. Cardiac and other peripheral tissues have L-type calcium channels. This explains the lack of cardiovascular side effects with pregabalin.

Fig-2: Structure of calcium channel



Dosage and administration:

For painful diabetic peripheral neuropathy, the maximum recommended dosage is 100 mg thrice a day. Because pregabalin is eliminated primarily by renal excretion, the dose needs to be reduced in patients with reduced renal function. For peripheral neuropathy, dosing should begin at 75 mg per day, and may be increased to 300 mg per day within a week based on efficacy and tolerability.

Pharmacokinetics

Pregabalin has consistent dose proportional pharmacokinetics

The mean elimination half-life of pregabalin is 6.3 hours, and is independent of dose and repeated administration. This consistent dose-proportional pharmacokinetics of pregabalin provides confidence in the prediction of dose-response relationship in clinical practice. Administration of pregabalin with food has no effect on its absorption (13).

Distribution, metabolism, and elimination

L-transporter is an important system which is responsible for transport of substances across the brain and gut. Pregabalin is a substrate of this system and hence crosses blood brain barrier rapidly. This property is essential for a drug that influences central nervous system activity.

In humans, pregabalin undergoes less than 2% metabolism. It is excreted unchanged by the kidneys. In patients with compromised renal function the dose of pregabalin needs to be reduced. In patients with creatinine clearance between 30 to 60 ml/minute, daily dose of pregabalin needs to be reduced by 50% when compared to patients with creatinine clearance more than 60 ml/minute.

Pregabalin versus gabapentin

Though pregabalin and gabapentin belongs to same group and possesses similar chemical structure, pregabalin has better pharmacokinetic properties.

Table-1: Pharmacological properties of pregabalin[7]

Property	Clinical significance
1. High affinity for α2δ receptor	New mechanism of action
2. No effect on GABA	No retinal or optic nerve toxicity
3. Linear dose proportional Cmax	Predictable level and dose response
4. Lack of protein binding	No drug interactions
5. Negligible metabolism	No drug interactions
6. Renal excretion (98% unchanged)	Dose reduction in renal impairment No hepatic effects
7. Rapidly cross blood brain barrier	Access to CNS site of action
Cmax – maximal plasma concentration	

Pregabalin lacks drug-drug interactions:

Pregabalin does not bind to plasma proteins and is not subjected to hepatic metabolism. Studies done on human liver microsomes have demonstrated that pregabalin does not affect the cytochrome P450 system.

These facts indicate that pregabalin is unlikely to cause pharmacokinetic drug interactions. This property is important when administering pregabalin with other anticonvulsant drugs.

Safety implications of pregabalin:

Pregabalin does not completely block calcium channel function or transmitter release, even at high concentration. This property could have important safety implications in case of drug overdose.

Alpha 2 delta ligands acts on N-type calcium channels, and have little effect on voltage gated calcium channels of heart (L-type), or other peripheral tissues. Hence, pregabalin has no effect on arterial blood pressure or cardiac function at therapeutic doses.

Clinical uses of pregabalin

1. Highly effective adjunctive therapy in the treatment of partial seizures
2. Chronic pain syndromes like, diabetic peripheral neuropathy, and post herpetic neuralgia.
3. Chronic anxiety disorder
4. Adjuvant in acute pain management

Since pregabalin possess anticonvulsant, sedative, analgesic, and anti-hyperalgesic properties, studies are being done on potential perioperative uses like pre-operative sedation, anxiolysis, reduced inter-operative opioid requirement, and attenuation of hemodynamic stress response to laryngoscopy and tracheal intubation.

Alpha 2 delta receptor seems to be involved in the phenomenon of neuronal hypersensitisation to noxious stimuli. Blunting of this hypersensitisation by pregabalin helps in reducing the intensity of post-operative pain and has got opioid sparing effect.

Side effects and precautions

Pregabalin is a well-tolerated, relatively safe drug with dose-dependent adverse effects which are mild to moderate and usually transient.

1. Dizziness (29%)
2. Somnolence (22%)
3. Dryness of mouth (9.1%)
4. Blurred vision (6.4%)
5. Edema (6.1%)
6. Weight gain (5.6%)
7. Abnormal thoughts (5.4%)

There are case reports of myoclonus, gynaecomastia, and a single case report of carpus callosum edema. Withdrawal of pregabalin after long term therapy should be gradual as it may potentiate seizure activity.

Pregabalin is contraindicated in patients with history of allergy to the drug or any of its components. FDA placed pregabalin in class C for pregnant patients. It is not recommended in pregnancy and breast feeding. Dose needs to be reduced in patients with reduced renal function.

PATIENT CONTROLLED ANALGESIA[8,9]

Widespread recognition of under treatment of acute pain by clinicians has led to the evaluation of practice guidelines for acute pain management by professional society like American society of anaesthesiologist (ASA). Anaesthesiologists who are very well aware of the importance of good pain control are the leaders in acute pain management services.

The various reasons for the inadequate control of pain includes the following reasons

1. Wide interpatient and intrapatient variability in the need for analgesics.
2. Variability in the plasma drug concentration, especially after intramuscular injections.
3. Delay in administration of analgesics.

Traditional intermittent injections of analgesic when required cannot compensate for these factors.

Patient controlled analgesia,

- Optimises delivery of analgesic drugs
- Overcome the problem of pharmacokinetic variability among patients

- When patient experiences pain, he administers a bolus and when pain reduced there are no further demands.

Patient controlled analgesia (PCA) is a method of offering the patients to self-administer the analgesic in a predetermined safe dosage as and when required. The route of administration and the choice of drug varies; intravenous PCA being the common mode.

Fig-3: Patient controlled analgesia device

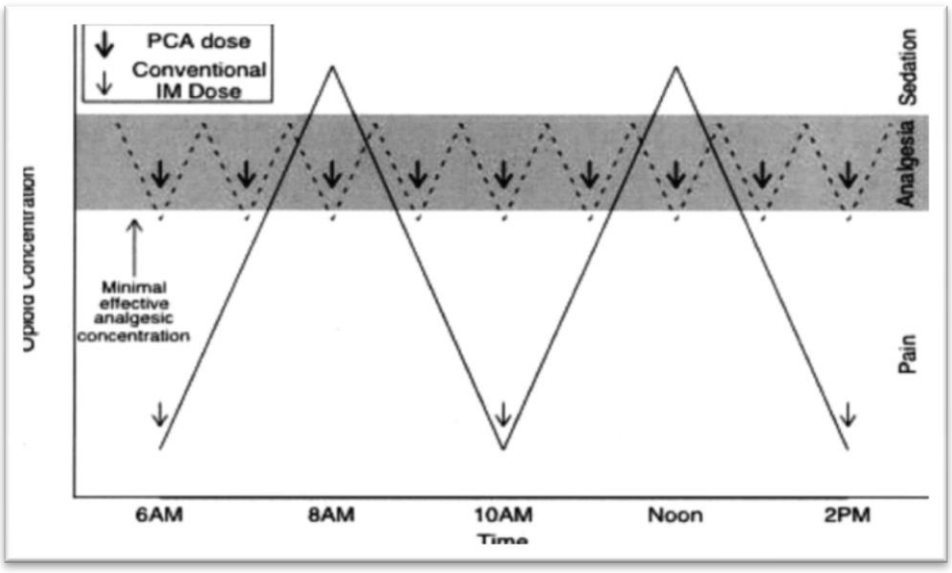
A PCA device can be programmed for several variables like

- Demand dose – an optimal demand dose is essential for efficient PCA

- Lock-out interval – most interval range from 5 to 10minutes
- Background infusion – generally not suggested for opioid naïve patients

Austin deserves the credit for first clarifying the pharmacological concept of PCA. The smallest plasma concentration of the drug at which analgesia occurs is the minimum effective analgesic concentration (MEAC) which marks the difference between pain and analgesia. PCA maintains the plasma concentration within the effective analgesic range without peaks and troughs as in intermittent analgesic regimen.

Fig-4: Minimum effective analgesic concentration



PCA provides,

- Better quality of analgesia
- Greater patient satisfaction
- No difference in incidence of adverse effects
- No difference in PACU or hospital stay

REVIEW OF LITERATURE

The hemodynamic response to laryngoscopy and tracheal intubation, its physiological basis, the importance to attenuate these circulatory changes, and the various pharmacological methods to attenuate this response are extensively studied.

Studies done on hemodynamic response to laryngoscopy and intubation

Reid and Brace[10]

In 1940, Reid and Brace suggested that irritant receptors are present in larynx, trachea, bronchi, and lungs. Mechanical stimulation of these receptors elicits a vasovagal response resulting in bradycardia, because both the afferent and efferent fibres were considered to be of vagal.

Burstein[11]

A decade later, Burstein and others using the same method of study in a large series of cases reached a different conclusion. They concluded that the majority of electrocardiographic changes during laryngoscopy and intubation were due to stimulation of cardioaccelerator fibres.

King.B.D, Harris LC, Greifenstein[12]

Since electrocardiograph cannot reflect the functional status of the heart, continuous arterial pressure and heart rate monitoring was done by B.D.King. He found that, laryngoscopy alone can cause a pressor response. Insertion of tube into trachea further augments this effect and in addition capable of producing arrhythmia. He also excluded the retention of carbondioxide as a cause of sympathetic stimulation as it was a delayed response and not as abrupt as the laryngoscopic stress response. Hypertension was found to be due to increase in cadiac output due to increase in myocardial contractility and venous return, and increase in arteriolar resistance. Tachycardia occurred by stimulation of cardio accelerator fibres.

Charles and Wycoff[13]

The hemodynamic response to laryngoscopy gained notice after the introduction of neuromuscular relaxants, as a part of balanced anesthesia. King and associates studied the stress response without the aid of muscle relaxants. Charles and Wycoff observed the influence of succinylcholine on the hemodynamic response to laryngoscopy. Succinylcholine produced transient rise in blood pressure and heart rate became more rapid. All these changes were not as abrupt as that caused by laryngoscopy, and returned to normal in one minute.

The sympathoadrenal reflex response

Prys-Roberts C, Greene L, Miloche[14]

Animal experiment done on cat by Timori and Widdicomb in 1969, demonstrated that the tachycardia and hypertension elicited by stimulation of respiratory tract was associated with enhanced neuronal activity in the cervical sympathetic efferent fibres.

Shribman AJ, Smith G, Achola KJ[15]

Compared plasma catecholamine level and the cardiovascular response to laryngoscopy alone and those due to laryngoscopy and tracheal intubation. There was significant and similar increase in arterial pressure, heart rate, plasma noradrenaline and adrenaline level following laryngoscopy with or without intubation. Intubation however was associated with significant tachycardia, which did not occur with laryngoscopy alone.

Derbyshire DR, Chmielewski A, Fell D[16]

Similar result was observed by Derbyshire, who reported increase in plasma catecholamine level concomitant with the hemodynamic response following laryngoscopy and intubation. Correlation between mean arterial pressure and catecholamine rise was significant when succinylcholine was used instead of pancuronium for intubation.

Morbidity caused by the hemodynamic stress response

Kovac AL[17]

The hemodynamic response to laryngoscopy and intubation increases the cardiovascular and central nervous system morbidity.

Low JM, Harvey JT, Prys-Roberts C[18]

Proved that hypertensive response to laryngoscopy was exaggerated and accompanied by markedly elevated plasma nor-epinephrine concentration in hypertensive patients.

These hemodynamic swings prove dangerous to hypertensive patients, whose heart might be damaged by the hypertensive disease.

John Bullington[19]

Studied the impact of advanced ageing on the hemodynamic response to laryngoscopy and shown that elderly patients have exaggerated sympathetic response to laryngoscopy accompanied by elevated plasma nor-epinephrine level. They had exaggerated hypertensive response and reduced chronotropic effect. He concluded that this could be because of reduced sensitivity of beta-1 receptors and normal alpha receptor sensitivity with advancing age.

Gabapentenoid group of drugs

Noor M. Gajraj[6]

Gabapentenoid group of drugs includes Gabapentin and Pregabalin. They are

relatively new group of drugs, which has got several clinical usefulness. Pregabalin is synthetic molecule, which is used as a highly effective adjuvant therapy in treatment of partial seizures, and in chronic pain syndromes like diabetic peripheral neuropathy, and post herpetic neuralgia.

Kugler AR[20]

Pregabalin pharmacokinetic properties have been investigated in 28 different pharmacology studies involving total of 472 subjects. They included dose ranging study from 1 mg to 300 mg. The results from these studies indicate that pregabalin has highly predictable and linear pharmacokinetics, with low interpatient variability.

Elinor Ben Mechanam[7]

Pregabalin is absorbed rapidly and extensively after oral dosing, with maximum plasma concentration occurring in approximately one hour after a single dose. The oral bioavailability is high at >90%, and is independent of the dosage.

Role of gabapentin on attenuation of laryngoscopic stress response

Sherhat Koc, Dilek Memis, Necdet Sut[21]

Compared the efficacy of gabapentin alone and in combination with dexamethasone in attenuation of the laryngoscopic stress response. An hour before induction, one group received 800mg gabapentin orally, other group received 8mg dexamethasone alone intravenously, and third group along with 800mg gabapentin, received 8mg dexamethasone. Induction and maintenance of anesthesia was done in a standard manner with propofol and remifentanyl infusion. Heart rate and blood pressure were recorded before induction, and after tracheal intubation. Intraoperative opioid requirement was documented. Hemodynamic parameters and visual analogue scale were recorded over 24hours. Any adverse effects of the drug were noted

Heart rate, blood pressure at 1minute, 3minutes, 5minutes, and 10minutes following intubation, remifentanyl consumption, and post-operative pain scores were all significantly lesser in patients who received 800mg gabapentin and 8mg dexamethasone. They did not observe any side effects like respiratory depression, vomiting, giddiness, during the first post-operative period. They concluded that the hemodynamic response to laryngoscopy and intubation was less in gabapentin 800mg alone group

than the control group and significantly reduced when gabapentin 800mg was combined with 8mg dexamethasone.

A. Fassoulakki, A. Melemeni, A. Paraskeva and G. Petropoulos[22]

This randomised placebo controlled study evaluated the effect of 1600mg gabapentin administered in four divided doses of 400mg each, starting on the noon of the day before surgery in patients undergoing abdominal hysterectomy under general anesthesia.

Anesthesia was induced with propofol and intubation facilitated with cis-atracurium 0.15mg/kg. They measured systolic, diastolic blood pressure and heart rate at baseline, 1, 3, 5, and 10minutes after intubation. They did not record the duration of each intubation and considered the Cormack Lehane grading as indication of difficulty of laryngoscopy. Patient's characteristics were compared with Student's t-test for unpaired observations. ANOVA with repeated measures were used to compare changes in blood pressure and heart rate. Systolic blood pressure differed with regard to group (p-0.003) and with regard to time (p-0.0001). Inter group comparison for each time point showed significantly higher systolic blood pressure values in control group. Diastolic blood pressure differed with respect to group (p-0.01) and with regard to time (p-0.0001). Inter group comparison for each time point showed significantly higher diastolic blood pressure values in control group. Heart rate did not

differ with regard to group (p-0.269) but differed with regard to time (p-0.0001). They concluded that gabapentin in the dose used attenuates pressor response to laryngoscopy and intubation. It has no effect on the changes in heart rate.

Usha Bafna, Vipin K Goyal, Ashish Garg[23]

Compared the efficacy of different doses of gabapentin on attenuation of pressor response to intubation. Patient undergoing elective surgeries under general anesthesia were divided into three groups. One group received 6oomg gabapentin, other group received 1000mg gabapentin administered 1hour prior to surgery, and were compared with placebo group.

General anesthesia was induced with thiopentone and intubation was facilitated with succinylcholine. Anesthesia was maintained with Isoflurane and 66% nitrous oxide in oxygen and atracurium 0.1mg/kg. Laryngoscopy and intubations were performed by experienced anesthesiologist and the duration of laryngoscopy was limited to minimum possible time.

Heart rate, arterial blood pressure was recorded. They did not score sedation and did not measure stress mediators such as endogenous plasma

catecholamines or cortisone, which they considered as limitation of the study.

Mean arterial pressure and heart rate were increased significantly after intubation in control and 600mg gabapentin group. There was significant decrease in mean blood pressure and heart rate in 1000mg gabapentin group. They concluded that 1000mg gabapentin administered an hour before induction significantly attenuated hemodynamic response to intubation.

Evaluation of pregabalin premedication

Paul F. White, Burcu Tufanogullari, Jimmie Taylor[24]

They tested the hypothesis that premedication with oral pregabalin would produce useful preoperative sedation and anxiolysis in a dose related manner. Its effect on post-operative pain relief was their secondary objective.

This dose ranging study compared placebo group, 75mg, 150mg, and 300mg pregabalin given 1hour before induction. Patient's level of anxiety, sedation, and pain were observed using 11 point verbal rating scale during intra-operative period and in PACU. Post-operative opioid requirement, occurrence of nausea and vomiting, the need for antiemetic, duration of PACU and hospital stay was recorded. They also did a seven

days follow up to record patient's quality of recovery scores, and late recovery outcomes.

Post-operative fentanyl requirement, duration of PACU and hospital stay did not differ among groups. Anxiety level remained unchanged. Pregabalin 300mg produced significantly higher sedation score at the pre-induction period and at 90 and 120 minutes after surgery compared with control group.

They concluded that pregabalin premedication produces perioperative sedation in a dose related fashion, but failed to reduce anxiety, post-operative pain, or improve the recovery after minor elective surgery.

Sundar AS, Rajeshkumar Kodali, Mahesh Vakamudi[25]

This clinical study evaluated and compared preoperative single dose pregabalin premedication to a placebo on attenuation of hemodynamic response to intubation, to assess perioperative requirement and side effects. Sixty adult patients undergoing off pump CABG were randomised into control group who received placebo capsule and study group who received 150mg pregabalin capsule 1hour before surgery.

The demographic data were comparable between the groups. Distribution of risk factors, like hypertension, diabetes, and history of

myocardial infarction in the two groups was not significant. The numbers of patients with regional wall motion abnormality between the groups were insignificant.

The baseline hemodynamic parameters were comparable between the two groups. The increase in heart rate was significantly higher in control group. A significant change in mean blood pressure was observed between the groups. It was higher in the control group. There were no significant differences in the post-operative fentanyl consumption.

This study observed that single dose oral pregabalin suppressed reflex tachycardia and hypertension due to laryngoscopy and tracheal intubation. The analgesic and opioid sparing effect was not apparent. It did not produce dizziness and visual disturbances.

Rastogi Bhawna, Kumkum Gupta, Prashant K Gupta[3]

They studied ninety normotensive patients aged 24 to 56 years and were divided into placebo group, 75mg pregabalin group, and 150mg pregabalin group. The drug was administered 1hour before induction. Anesthetic technique was standardised. Pre-operative sedation level, hemodynamic parameters, and post-operative side effects were studied.

Preoperative sedation level was higher in premedication groups. Significant increase in heart rate and mean arterial pressure were seen in

placebo group and pregabalin 50mg group. The attenuation of heart rate and mean blood pressure were significant with 150mg pregabalin. Heart rate changes were not significant in any of the groups.

They concluded that premedication with pregabalin sedated the patients adequately in a dose related manner. The hemodynamic stress response to laryngoscopy was significantly attenuated by 150mg pregabalin without increase in side effects.

Kumkum Gupta, Deepak Sharma, Prashant Gupta[26]

They compared placebo with 150mg pregabalin and 300mcg clonidine on attenuation of pressor response to laryngoscopy and intubation in patients undergoing elective laparoscopic cholecystectomy. The test drugs were administered 75 to 90minutes prior to surgery as oral premedication. Group comparison was done for preoperative sedation, anxiety level along with changes in heart rate and mean blood pressure changes prior to and after induction, after laryngoscopy, pneumoperitoneum, and extubation. Intraoperative drug requirements and incidence of side effects were studied.

They concluded that 150mg pregabalin and 200mcg clonidine produced sedation and anxiolysis. It attenuated hemodynamic changes to laryngoscopy and tracheal intubation without causing in side effects.

Antihyperalgesic effect of pregabalin

There are several studies done on the efficacy of pregabalin as good adjuvants in acute pain management. The opioid sparing effect pregabalin is because of the blocking of alpha 2 delta subunit of calcium channel, thereby preventing the hypersensitisation phenomenon.

These studies compared different doses of pregabalin administered either as single dose or as multiple doses. Reduction of post-operative pain scores indicates good quality of analgesia, whereas reduction in total opioid dose consumed indicates opioid sparing effect.

Mathieson O, Jacobsen LS, Holm HE[27]

Mathieson investigated analgesic efficacy of pregabalin and dexamethasone in patients undergoing total hip replacement surgery under spinal anesthesia. Hundred and twenty patients were randomly allocated into three groups who receive placebo or 300mg pregabalin alone or with dexamethasone 8mg. patients received 1gm paracetamol an hour before surgery and later in post-operative period every 8hours. Patients were provided patient controlled (PCA) analgesia with2.5mg bolus of morphine.

Morphine requirement in first 24hours of surgery was reduced by 50% in patients who received pregabalin alone and with dexamethasone.

Nausea and vomiting was less in dexamethasone group. Pregabalin produced excessive sedation at 300mg dosage. Addition of dexamethasone did not provide any additional benefits regarding pain control but reduced nausea and vomiting.

R. Jokela, Ahonen J, Tallgren M[28]

Their study was based on the fact that multimodal analgesia improved the quality of post-operative pain management. They invested patients undergoing day-care laparoscopic gynaecological surgery. Pregabalin premedication in a dose of 75mg and 150mg were compared with 5mg diazepam. The post-operative analgesia was provided with 400mg Ibubrufen twice daily with intravenous fentanyl on request at recovery room. Paracetamol with codeine tablets after recovery room.

The visual analogue scale for pain at rest, at motion, on coughing and the amount of analgesics required over 24hours of after surgery were recorded. The area under curve (AUC) for VAS for pain at rest and at motion was significantly less with 150mg pregabalin. There was no difference in the amount of analgesics consumed.

They concluded that pregabalin premedication improved quality of analgesia in the early post-operative period after laparoscopic

gynaecological surgery. 150 mg pregabalin did not reduce the amount of analgesic drug.

Sion M. Burke[29]

They evaluated patients who underwent lumbar discectomy regarding long term pain and the effect of pregabalin premedication on it. They tested the hypothesis that many patients continue to experience pain even 3 months after discectomy. Pregabalin, a membrane stabilizer, may decrease perioperative central sensitization and subsequent persistent pain.

Forty patients undergoing lumbar discectomy received either placebo or 300mg pregabalin at 90minutes pre-operatively and 150mg at 12 and 24 hours post-operatively. Change in present pain intensity from pre-operatively to 3 months post-operatively.

They concluded that administration of pregabalin during peri-operative period was associated with less pain intensity and improved functional outcome 3 months after lumbar discectomy.

P.W.H.Peng[30]

Peng evaluated the efficacy of low dose pregabalin on the analgesic efficacy, adverse effects, and recovery characteristics in patients undergoing laparoscopic cholecystectomy.

He compared 50mg and 75mg of pregabalin with placebo administered 1hour before surgery and every 12 hours post-operatively for a total of 3 doses. Numeric pain score, analgesic requirement, adverse effects, and recovery score (QoR-40) were studied in the early post-operative period (12hours).

The pain score was lesser in pregabalin75mg group in first 90minutes after surgery and with50mg pregabalin up to 30 to 45minutes after surgery when compared to placebo. The analgesic requirement, side effects, and recovery profile were comparable between the groups.

They concluded that 75mg pregabalin provided limited benefits in the post-operative period.

MATERIALS AND METHODS

Study design : Prospective, randomised, double blinded study

Study population: 60 patients

Institutional ethical committee approval obtained

Inclusion criteria:

- Age – 20 years to 60 years
- ASA – 1 and 2, normotensive patients
- Surgery – Elective abdominal surgery
- Requiring general anesthesia with endotracheal tube
- Who gives consent for the study

Exclusion criteria:

- Anticipation of difficulty in airway management, and when the duration of laryngoscopy and intubation exceeded 30 seconds.
- Patients with seizure disorder.
- Uncontrolled systemic illness.
- Patients on pregabalin or gabapentin therapy.
- History of known allergy to pregabalin.
- Pregnancy.

Materials:

- Pregabalin capsules.
- Similar looking placebo capsules.
- Patient controlled analgesia pump.
- Pain assessment chart.

Primary outcome measures:

- Ramsay sedation scale.
- Heart rate, systolic, diastolic, mean blood pressure at baseline, 1, 3, 5, 10, 15minutes after laryngoscopy and intubation.
- Recovery characteristics from general anesthesia.

Secondary outcome measures:

- Post-operative fentanyl requirement.
- Any adverse effects to pregabalin.

Study protocol:

1. All the patients were visited the evening before surgery. They were explained about the study methods, the visual analogue scale chart, methods to use patient controlled analgesic pump, and were provided with information sheet.

2. Only those who gave consent for the study and satisfied inclusion criteria were included. The night before surgery patients received Ranitidine 150 mg and Alprazolam 0.5 mg per oral.

3. Randomisation – sixty patients were allocated randomly into two groups of 30 each. Group-C received placebo capsules and Group-P received 150 mg pregabalin, one hour before induction. Both the investigator and the observer were not aware of the groups till the end of the study.

4. The morning of surgery, patients received Ranitidine 50 mg and Metoclopramide 10 mg, intravenously, and the test drug was given orally with

sips of water, one hour before induction. Both the group allocation and administration of test drug were done by an anesthetist who was not involved in the study.

5. Sedation level – The level of sedation was recorded prior to test drug administration, one hour later, and prior to premedication. At post anesthesia care unit (PACU), sedation level was assessed at baseline, 1hour, 2hours, 4hours, 8hours, and at 12hours after surgery.

Table-2: Ramsay sedation scale

• **Patient anxious and agitated or restless, or both**
• **Patient co-operative, oriented, and tranquil**
• **Patient responds to commands only**
• **Sedated with brisk response to stimulus**
• **Sedated with sluggish response to stimulus**
• **Sedated with no response to stimulus**

(Stimulus – light glabellar tap or loud command at ears)

6. Heart rate, systolic, diastolic, and mean blood pressure were recorded at baseline on arriving to operating table, after premedication, after induction, 1 minute, 3 minutes, 5 minutes, and 10 minutes after laryngoscopy and intubation. Bradycardia defined as heart rate less than 60 per minute, was treated with Atropine 0.6 mg intravenously. Hypotension defined as systolic blood pressure less than 90 mmHg, was treated 200 ml bolus infusion of crystalloid solution and Ephedrine 3 mg, intravenously.

7. Laryngoscopy and intubation was performed by an anesthetist who had not less than 2 years of experience in laryngoscopy. Duration taken to do laryngoscopy and intubation, and the grade of laryngoscopic view were recorded. When the duration exceeded 30 seconds, the case was excluded from the study.

8. The characteristics of recovery from general anesthesia, and the occurrence of nausea, vomiting, shivering, bradycardia (heart rate less than 60/minute), hypotension (systolic blood pressure less than 80mmHg), and respiratory depression (defined as respiratory<10/minute, SpO2<90%) were documented.

9. All the patients were shifted to post anesthesia care unit (PACU)

10. Pain relief was provided with intravenous patient controlled analgesia with fentanyl.

Anesthetic management:

Surgery was done under general anesthesia with endotracheal tube and controlled ventilation. Ringer lactate was started at 100 ml/hour through 18G intravenous cannula. Heart rate, SP02, non-invasive blood pressure, electrocardiographic monitoring was done.

Pre-medication was done with glycopyrrolate 0.2 mg, midazolam 0.04 mg/kg, and fentanyl 2mcg/kg intravenously, 5 minutes before

induction. Induced with thiopentone 5mg/kg i.v and intubation facilitated by succinylcholine 1.5mg/kg.

Anesthesia was maintained with 2% sevoflurane, in a mixture of 66% nitrous oxide in oxygen. Ventilation controlled with closed circuit, facilitated by increments of 0.02mg/kg vecuronium. Vital signs were monitored every 5 minutes during intra-operative period and intravascular volume replacement was done appropriately. At the end of the procedure residual neuro muscular blockade was reversed with neostigmine 50mcg/kg with glycopyrrolate 0.5mg. After complete recovery, extubation was done.

Post-operative management:

On arrival to PACU, all the patients were offered patient controlled analgesia with intravenous fentanyl. Heart rate, blood pressure, and SPO2 were monitored. Level of sedation was assessed with Ramsay sedation scale, and the magnitude of pain was assessed with 10 points visual analogue scale periodically at baseline, 1 hour, 2hours, 4 hours, 8 hours, and 12 hours after surgery.

A separate i.v access was used for PCA pump. Hemodynamic parameters were recorded regularly and oxygen saturation monitored. Patients were observed for any adverse effects of fentanyl, proper functioning of PCA pump, break through pain, and the need for additional doses of fentanyl.

PCA protocol:

- Drug - Fentanyl
- Concentration - 10 microgram/ml
- Basal infusion - Nil
- Demand dose - 2.5ml (25mcg)
- Lock-out interval - 15 minutes

Whenever the patient had VAS of 4 or more, an additional dose of 25mcg of fentanyl was given intravenously. The fentanyl requirement for the first 12 hours of surgery was documented. The total requirement over 12 hours was calculated by adding total demand doses and additional doses made. The frequency of additional dose requirement was also compared between the two groups.

Study population size and statistical analysis:

Statistician was consulted with pilot study report of 5 cases in each group. The hypothesis testing of two means showed the sample size needed was 13, for the power of study to be 0.8 with alpha error of 5. Considering the number of patients who drop out from the study, the sample size was fixed at 30 in each group.

The statistical analysis was done using SPSS software, version 12. The mean and standard deviation calculated using student T test, and the significance calculated by chi-square test. P-value less than 0.05 was taken as significant, and less than 0.01 as highly significant.

RESULTS

The study was done in 60 patients of both sexes in the age group of 20 to 60 years, belonging to ASA class-1 and ASA class-2, undergoing elective abdominal surgery under general anesthesia with endotracheal tube. The patients were categorised into two groups.

Group-C - Placebo

Group-P - pregabalin

Statistical analysis

We did statistical analysis of the data collected using Microsoft Excel, and SPSS software. Student t-test and Chi-square test were used as appropriate. P value less than 0.005 was taken as significant and value less than 0.001 was taken as highly significant.

Demographic profiles

The demographic profiles like age, sex, and weight, and the ASA status, are comparable between the two groups (Table-1). No statistical significance is found when comparing these factors between the two groups.

Table-1: Demographic profiles, and ASA status

Demographic profile	Group-C	GROUP-P	p-value
Age (years)	37.87 ± 6.75	34.70 ± 8.36	0.112
Sex (M:F)	13:17	12:18	1.000
Weight (Kg)	59.80 ± 5.93	59.00 ± 9.09	0.688
ASA class 1: 2 , (n)	20:10	20:10	1.000

Fig-5 : Comparison of demographic data

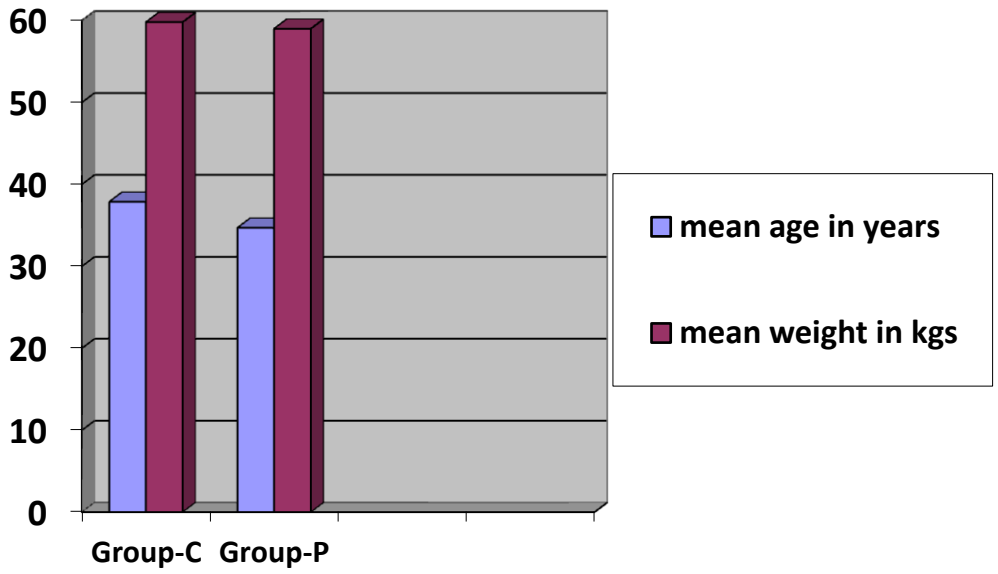


Fig- 6: Comparison of demographic data

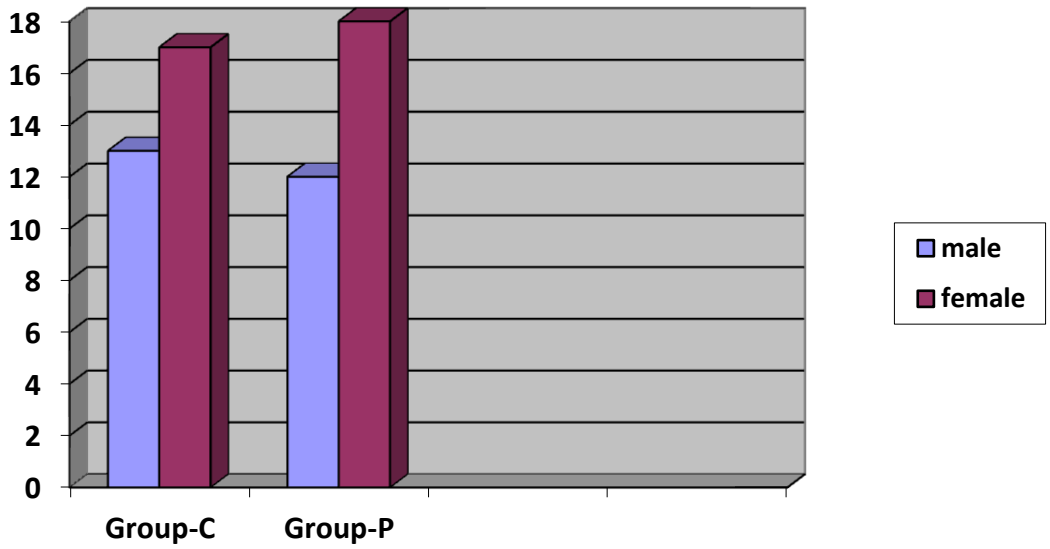
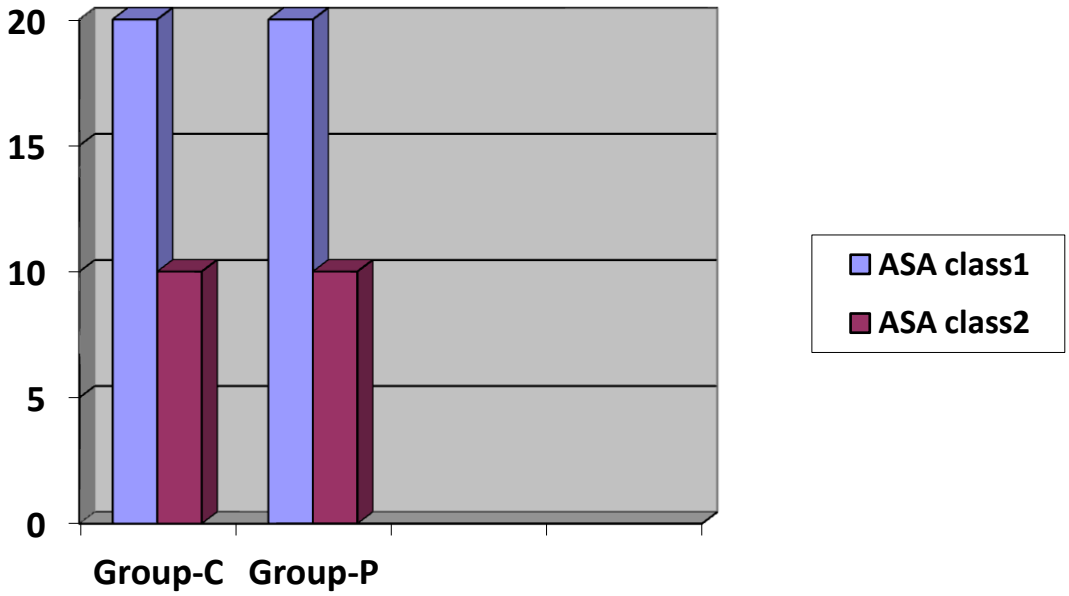


Fig-7: Comparison of demographic data



Nature and duration of surgery

The types of surgery are equally distributed among the two groups (Table-2). The mean duration of surgery is comparable. There is no statistically significant difference in these factors. In both control group and pregabalin group, the mean duration of laryngoscopy are comparable.

Table-2: Nature, and duration of surgery

	Group-C	**Group-P**
Open cholecystectomy, number (%)	6 (20.0%)	7 (23.3%)
Incisional hernia	7 (20.0%)	6 (23.3%)
Open appendicectomy	7 (23.3%)	6 (20.0%)
Paraumblical hernia repair	3 (10.0%)	3 (10.0%)
Abdominal hysterectomy	3 (10.0%)	4 (13.3%)
Epigastric hernia repair	4 (13.3%)	4 (13.3%)
Duration of surgery, mean(minutes)	90.07	92.33

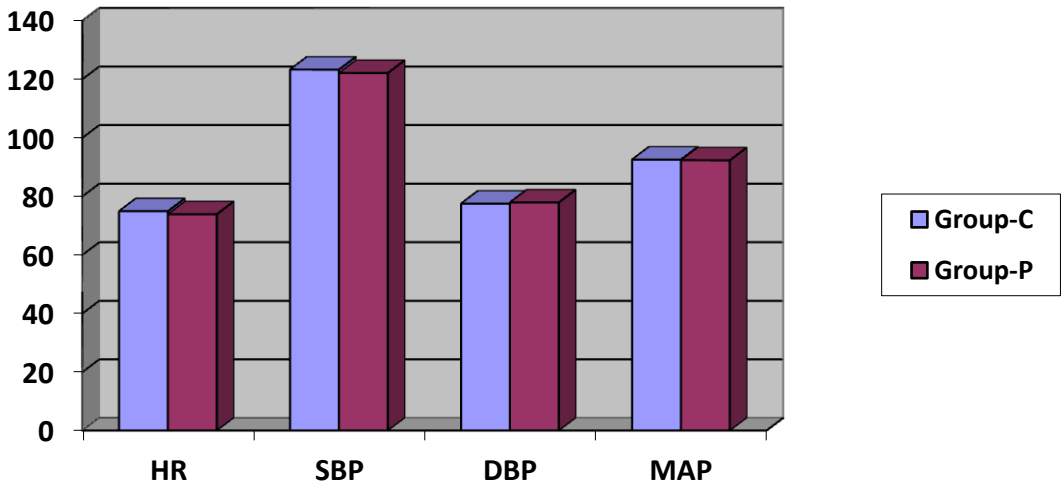
Baseline parameters

Baseline hemodynamic parameters are comparable between the two groups. There is no statistically significant difference between the groups.

Table-3: Baseline hemodynamic parameters in mean±SD

Parameter	Group-C	Group-P	p-value
Heart rate	74.90±4.49	73.87±6.51	0.479
Systolic blood pressure	123.27±8.294	122.10±8.294	0.639
Diastolic blood pressure	77.50±6.157	77.90±5.573	0.793
Mean blood pressure	92.53±7.417	92.30±5.754	0.892

Fig-8: Comparison of baseline hemodynamic parameters



Heart rate changes:

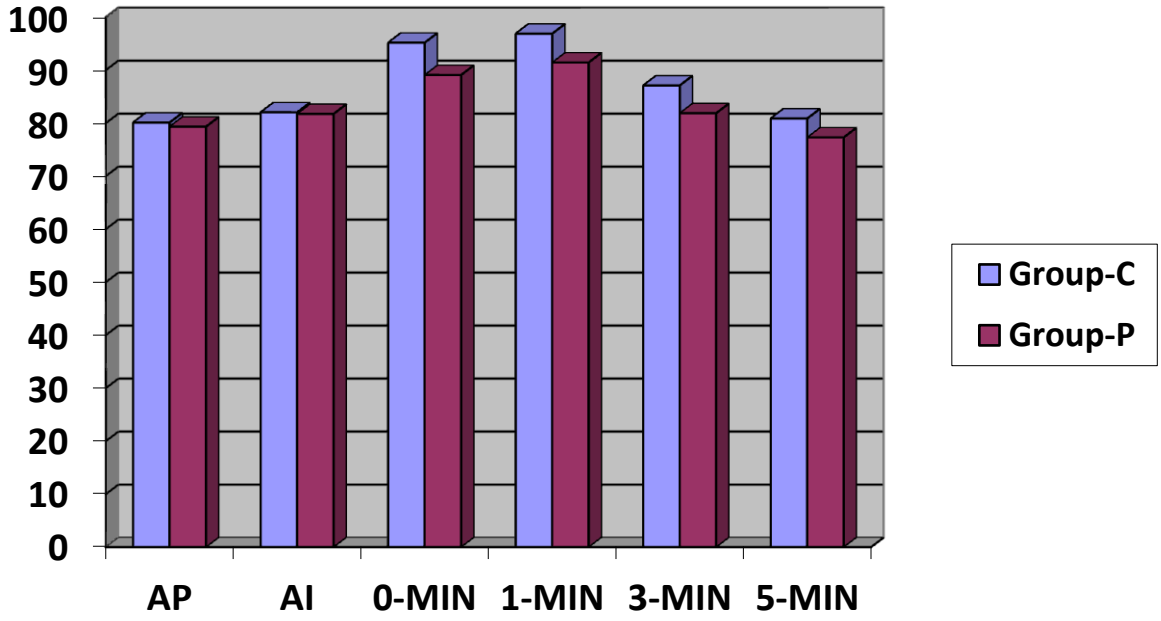
There was no significant difference in heart rate at baseline, before and after induction. In both the groups, heart rate raised at 1minute, 3minutes, and 5minutes following laryngoscopy and intubation. The raise in heart rate is significantly less in pregabalin group when compared to control group. The raise in heart rate normalised 5 minutes after laryngoscopy and intubation in both the groups (Table-3).

Table-4: Heart rate changes during anesthesia (mean±SD)

	Group-C	**Group-P**	**p-value**
After premedication	80.10 ± 5.59	79.33 ± 7.10	0.644
After induction	82.03 ± 5.26	81.73 ± 5.28	0.826
After intubation (0min)	95.17 ± 7.83	89.07 ± 6.98	0.002 (#)
1 minute	96.87 ± 8.45	91.43 ± 8.55	0.016 (#)
3 minutes	87.10 ± 8.47	81.87 ± 8.21	0.018 (#)
5 minutes	80.87 ± 8.24	77.30 ± 7.23	0.080
# - p-value highly significant			

Deviation of heart rate from baseline

Fig-9: Heart rate changes in mean±SD



AP-after premedication, AI-after induction, 0minute, 1minute, 3minutes, and 5minutes after laryngoscopy and intubation.

Deviation of blood pressure from baseline

There was no significant difference in systolic, diastolic, and mean blood pressure at baseline, before and after induction. But there was statistically significant attenuation of systolic and diastolic blood pressure in pregabalin group at o minute, 1 minute, and 3 minutes after intubation. The attenuation of mean blood pressure was highly significant in pregabalin group, when compared to the control group.

Table-5: Systolic blood pressure changes in mmHg (mean±SD)

	Group-C	Group-P	p-value
After premedication	120.53±8.565	118.80±8.058	0.423
After induction	115.13±11.617	111.57±10.295	0.213
After intubation (0min)	147.50±20.080	131.13±15.976	0.001 (#)
1 minute	151.37±21.787	134.47±16.137	0.001 (#)
3 minutes	129.13±15.741	117.13±16.126	0.005 (#)
5 minutes	122.23±12.894	117.80±11.090	0.159

- p-value highly significant

Fig-10: systolic blood pressure changes

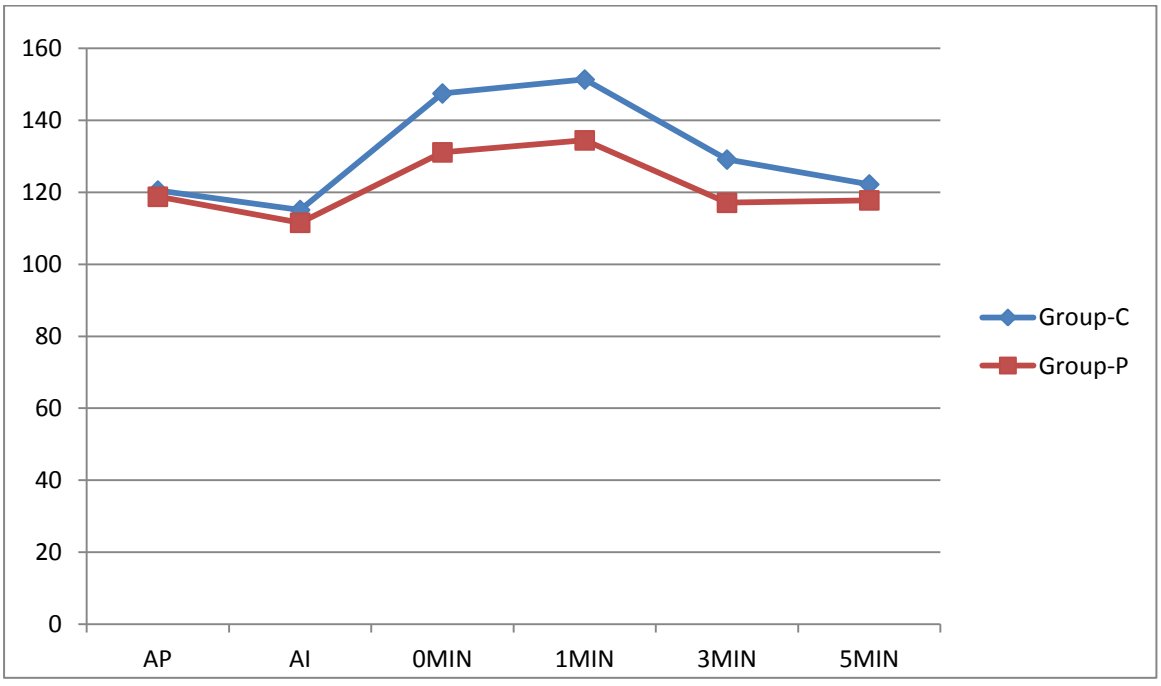


Table-6: Diastolic blood pressure changes in mmHg (mean±SD)

	Group-C	Group-P	p-value
After premedication	75.90±6.157	77.07±5.552	0.478
After induction	72.87±7.855	70.03±5.623	0.114
After intubation (0min)	97.00±14.648	87.67±11.137	0.007 (#)
1 minute	98.90±14.033	90.50±10.979	0.012 (#)
3 minutes	83.87±10.275	76.23±11.413	0.009 (#)
5 minutes	81.00±9.248	77.33±6.999	0.089

- p-value highly significant

Fig-11: changes in diastolic blood pressure

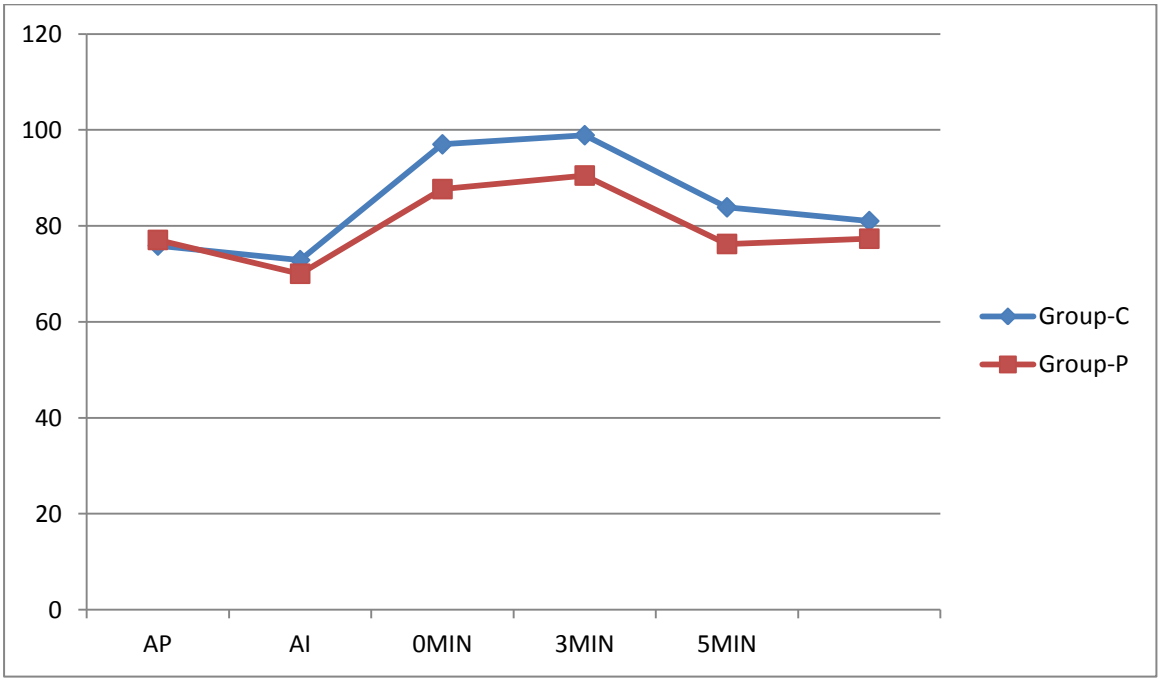
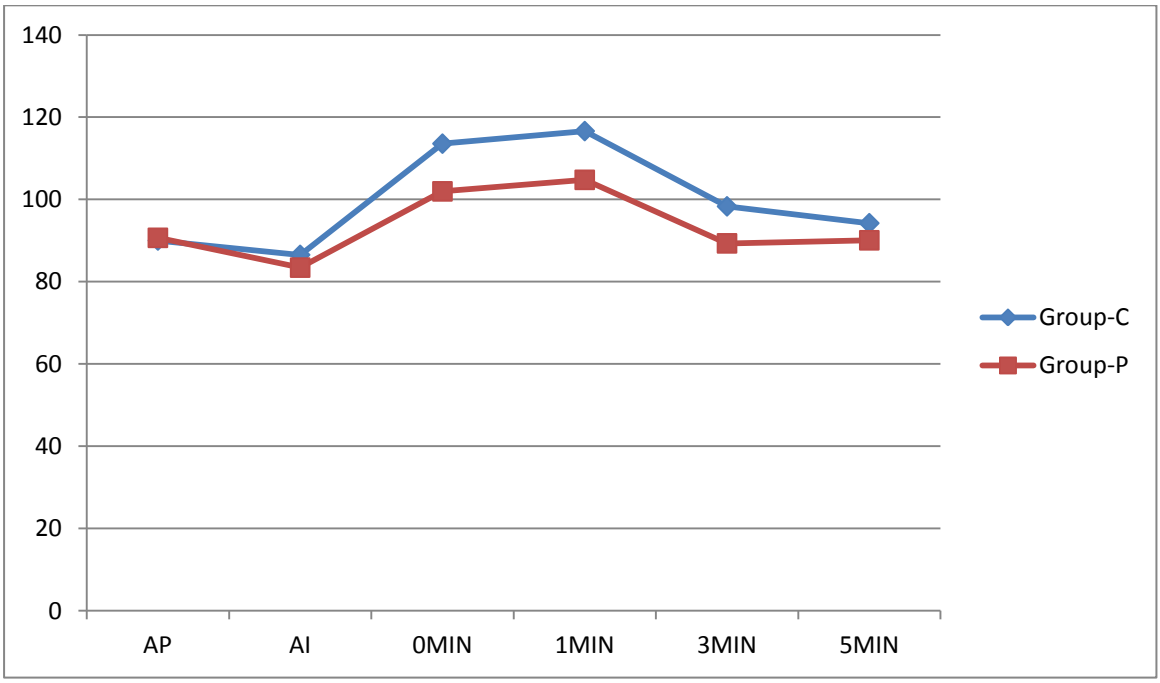


Table-7: Mean blood pressure changes in mmHg (mean±SD)

	Group-C	Group-P	p-value
After premedication	90.03±7.275	90.67±5.933	0.713
After induction	86.53±8.936	83.43±6.290	0.126
After intubation (0min)	113.57±15.822	101.97±12.339	0.002 (#)
1 minute	116.63±17.553	104.77±12.414	0.004 (#)
3 minutes	98.33±11.778	89.33±12.788	0.006 (#)
5 minutes	94.23±10.037	90.07±8.026	0.081

- p-value highly significant

Fig-12: Changes in mean blood pressure



Ramsay sedation scale and duration of intubation:

The mean duration of laryngoscopy and intubation in Group-C was comparable with that in Group-P. The patients in pregabalin group were sedated with brisk response to stimulus. The mean Ramsay sedation scale in Group-P before evaluated 1 hour after pre5gabalin administration was higher when compared to Group-C, with high statistical significance (Table-7).

Table-8: RSS after 1hour, and duration of laryngoscopy and intubation

	Group-C	**Group-P**	**p-value**
RSS (mean±SD)	2.00±0.00	3.17±0.699	0.000
Laryngoscopy (seconds)	10.10±1.989	10.10±1.749	1.000
(RSS – Ramsay sedation scale)			

Visual analogue scale for pain at rest:

The mean visual analogue scale (VAS) for pain at rest evaluated at baseline, 1hour, 4hours, 8hours of receiving patients at PACU, were comparable between the two groups, except at 2hours, and 12hours when Group-P had significant less VAS for pain at rest (Table-8).

Table-9: Visual analogue scale for pain at rest

VAS (mean±SD)	**Group-C**	**Group-P**	**p-value**
Baseline	6.67±1.061	6.43±1.194	0.427
1 hour	3.77±1.194	3.17±1.262	0.064
2 hours	2.90±0.548	2.57±0.626	0.032
4 hours	3.47±1.279	2.90±0.995	0.060
8 hours	3.33±0.959	2.87±0.937	0.062
12 hours	2.70±0.535	2.33±0.479	0.007

Post-operative sedation level:

The patients in pregabalin group were more sedated than that in control group, especially in the first two hours of post-operative period. They responded briskly to stimulus. The sedation level did not interfere in evaluating the Visual analogue scale for pain. The median Ramsay sedation scale were …….. at baseline, 1hour, and 2hours respectively, and the difference in sedation level was highly significant between the groups.

Table-10: Sedation level at PACU

RSS at PACU	**Group-C**	**Group-P**	**p-value**
Baseline	1.70±0.466	2.87±0.681	0.000 (#)
1 hour	2.07±0.254	3.40±0.675	0.000 (#)
2 hours	2.30±0.466	3.43±0.568	0.000 (#)
4 hours	2.60±0.536	2.83±0.747	0.177
8 hours	2.37±0.490	2.37±0.490	1.000
12 hours	2.23±0.430	2.30±0.466	0.567
# - p-value highly significant			

Adverse effects related to pregabalin and fentanyl:

The mean time to recovery of the patients from general anesthesia, for the return of response to simple verbal commands after last skin suturing was 11.4 minutes in control group and 12 minutes in pregabalin group. There was no delay in recovery in pregabalin group, the difference was statistically not significant. The incidence of nausea and vomiting was similar in both the groups. There was no incidence of bradycardia, hypotension, pruritis, and respiratory depression in both the groups. None of the patients in both groups had these adverse effects.

Table-11: Pregabalin and fentanyl related adverse effects

Events	**Group-C**	**Group-P**	**p-value**
Time to recovery (minutes) (mean±SD)	11.40±1.545	12.00±1.486	0.131
Nausea, vomiting, n (%)	19(63.3%)	19(63.3%)	1.000
Bradycardia (n)	0	0	-
Hypotension (n)	0	0	-
Respiratory depression (n)	0	0	-
Pruritis (n)	0	0	-

Post-operative PCA fentanyl requirement:

Additional fentanyl doses:

Apart from patient controlled fentanyl, 26 patients (86.7%) out of 30 in pregabalin group did not require any additional bolus doses of fentanyl, and 4 patients (13.3%) needed 1 additional dose. In control group, out of 30 patients, 13 patients (43.3%) required 1 additional dose, 1 patient (3.3%) required 2 additional doses, and 16 patients (53.3%) required no additional doses. The additional fentanyl requirement was significantly less in pregabalin group with p-value of 0.012 (Fig-1).

Total fentanyl requirement in first 12 hours:

When compared to group-C, group-P had highly significant less requirement of fentanyl during the post-operative period. The total of loading dose, demand doses, and additional doses of fentanyl was 317 microgram in control group, and it was 204 microgram in pregabalin group over first 12 hours after surgery. This reduced fentanyl requirement in pregabalin group had high statistical significance, with p-value of 0.000 (Fig-2).

Fig-13: Number of additional doses of fentanyl

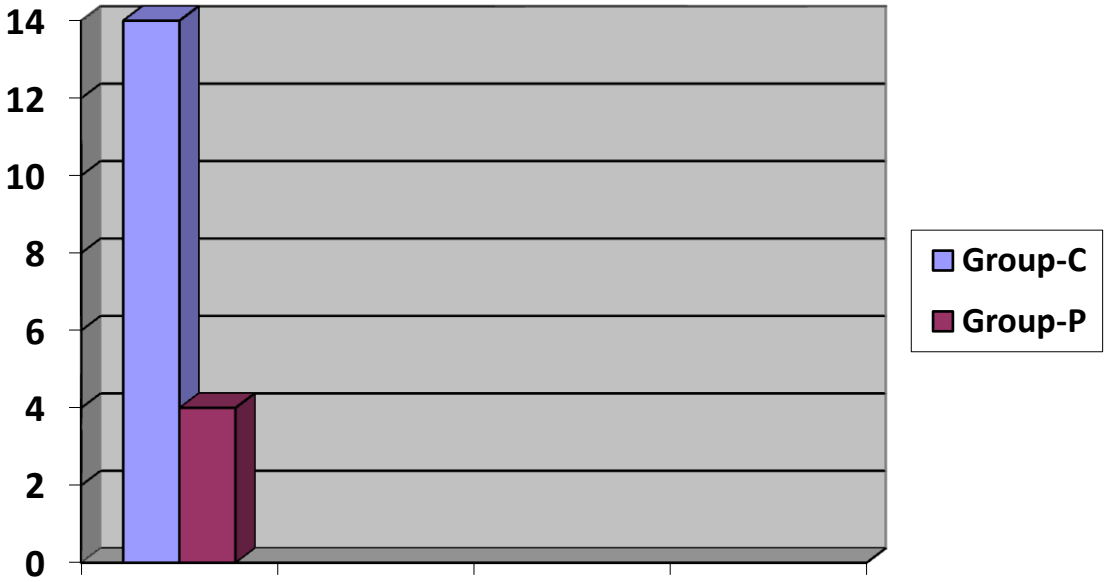
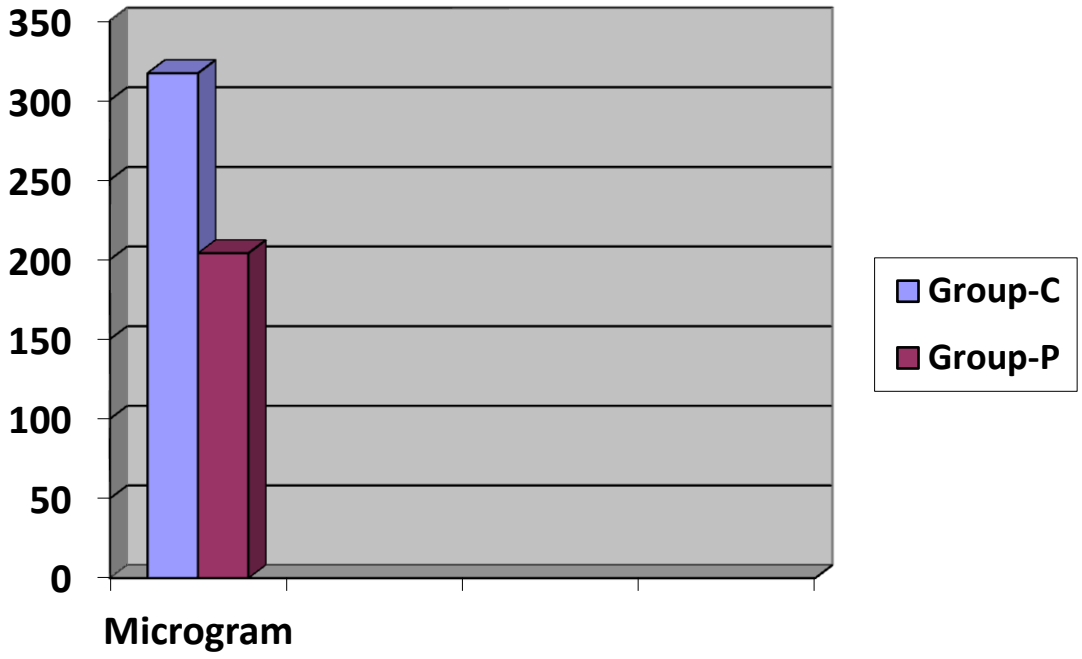


Fig-14: Total fentanyl requirement in micrograms



DISCUSSION

This study evaluated the effectiveness of premedication with a single dose of pregabalin administered orally one hour before induction on attenuation of hemodynamic stress response to laryngoscopy and intubation. The possibility of preemptive effect of pregabalin on post-operative patient controlled fentanyl requirement was also evaluated. Pregabalin premedication produced useful pre-operative sedation which did not prolong the recovery time from general anesthesia. The post-operative patient controlled fentanyl requirement was significantly reduced. Pregabalin did not produce cardiovascular side effects like bradycardia or hypotension. There was no respiratory depression or pruritis. However patients remained sedated for first 2 hours in PACU with brisk response to verbal commands.

Laryngoscopy and tracheal intubation elicits transient but harmful hemodynamic stress response. Tachycardia and hypertension are frequent complications during laryngoscopy and intubation, which occurs due to reflex sympathoadrenal response. Increase in serum catecholamines concomitant with laryngoscopy and the observations that beta receptor blockade attenuated the pressor response further confirmed the reflex

sympathoadrenal response as a possible mechanism for the stress response.[31]

This hemodynamic response is associated with increased incidence of myocardial ischemia, infarction, and dysrhythmias. Hypertensive patients and elderly people have exaggerated response and consequent increase in morbidity and mortality. Hence, this pressor response has to be attenuated by some pharmacological techniques.[19]

Intravenous lignocaine in a dose of 1.5 mg/kg given 90 seconds before induction attenuated pressor response but failed to attenuate tachycardia. Fentanyl 0.5 to 1 mcg/kg or remifentanyl 1 mcg/kg reduced pressor response but has the disadvantage of occurrence of bradycardia. More recently remifentanil has been studied and found to have attenuated pressor response but was associated with bradycardia in patient who have not received glycopyrrolate, and occurrence of hypotension.[32]

Gabapentin is a gabapentenoid drug with anticonvulsant, sedative, anxiolytic and analgesic properties. Gabapentin had been studied on attenuation of laryngoscopic pressor response and its effect on opioid sparing. Fassoulaki administered total of 1600mg gabapentin as a serial of four doses and found to attenuate pressor response but not tachycardia with intubation.

Both gabapentin and pregabalin has similar chemical structure and both acts on alpha 2 delta subunit of neuronal calcium channels. But pregabalin has better pharmacological profiles than gabapentin in that pregabalin has predictable onset time with peak effect in 1 hour and >90% oral bioavailability. In their study Sundar et al concluded that 150mg pregabalin attenuated reflex tachycardia and hypertension related to laryngoscopy and intubation which in concurrence with our study.[25]

The dose of pregabalin preferred in this study was based on a dose ranging study done by Paul F. White et al, in which 75mg, 150mg, and 300mg dose of pregabalin were compared. They found excessive sedation with 300mg dose. Further, Rastogi Bhawna et al in their study found 75mg pregabalin did not effectively attenuate the pressor response.[3] P.W.H.Peng postulated that multiple small doses of pregabalin could reduce post-operative opioid requirement. He found multiple doses of 75mg pregabalin reduced pain scores with limited benefits in the first 90 minutes after surgery. Analgesic requirement was the same.[30]

Based on these studies the optimal dose of pregabalin was decided to be 150mg which could attenuate pressor response without excessive perioperative sedation.

When studying the efficacy of a drug to attenuate laryngoscopic pressor response, the anesthetic technique employed affects the result of

the study. In this present study tachycardia occurred in both the groups, but the magnitude of increase was less with pregabalin premedication. This result is in contradiction to that of Fassoulaki who observed no difference in heart rate with gabapentin.[22]

This difference in result could be because of the anesthetic technique, where they induced with propofol which tend to cause bradycardia masking the effect of gabapentin on heart rate. In our study, both the thiopentone induced and succinylcholine fasciculation induced tachycardia could have resulted in tachycardic response in both the groups. But the increase in heart rate was less in pregabalin premedicated patients.

The exact mechanism of attenuation of pressor response by pregabalin is not known. The blocking of neuronal calcium channels could be the possible mechanism that it may act in a similar manner by which calcium channel blockers controls the hemodynamic response. Primary culture of bovine adrenal chromaffin cells was used by Robert D Todd to study the effects of gabapentin on adrenal cells. He observed that gabapentin reduced release of catecholamine from adrenal chromaffin cells without altering its contents. Gabapentin did not restrict the entry of calcium into cells but calcium was less effective in causing vesicle fusion.[33]

The duration of laryngoscopy, grade of laryngeal view can affect the result of the study. In this study the laryngoscopy was done by anesthesiologist who had at least two years of experience. When the time taken to do laryngoscopy and tracheal intubation exceeded 30 seconds, patients were withdrawn from the study. The grade of laryngeal view and duration of laryngoscopy were comparable between the two groups.

Induction of general anesthesia was done in this study with thiopentone sodium which can cause tachycardia and the fasciculation caused by succinylcholine can also increase heart rate. This could have masked the effect of pregabalin on heart rate. Though the magnitude of tachycardia was less in pregabalin group, both the groups had increase in heart rate from the baseline value.

The level of pre-operative sedation was significantly higher with pregabalin premedication which did not prolong the recovery process from general anesthesia. This can be an advantage in the pre-operative period, but preanesthetic sedation can interfere with the randomisation of groups.

Evaluation of anxiety level, measurement of serum catecholamine level, observation of intra-operative fentanyl requirement would have provided more information. This was not done in this present study.

In this study, patient controlled analgesia with intravenous fentanyl was used for post-operative pain relief. This technique helped in estimating the fentanyl requirement accurately than using intermittent bolus doses. Non-steroidal anti-inflammatory drug was not given in this case. The visual analogue scale for pain at rest was comparable with placebo group, which points out to no improvement in the quality of analgesia with pregabalin premedication. This finding is in contradiction with the observation made by Jokela.R and colleagues that VAS score was lesser in patients who received 150mg pregabalin with 800mg Ibubrufen, which indicates better quality of analgesia.[28]

This difference could be because of difference in the rescue analgesic method used. With multimodal analgesia the quality of pain relief could have been better in this study.

The pregabalin premedicated patients required 4 additional doses and a total of 204 microgram of fentanyl. Whereas placebo group required 14 additional doses and a total of 317 microgram of fentanyl over the first 12 hours after surgery. None of the patients in both groups had bradycardia, hypotension, respiratory depression, or pruritis.

Mathieson concluded that 300mg pregabalin reduced post-operative morphine requirement by 50% but with greater sedation, nausea and vomiting.[27] Whereas in our study 150mg pregabalin produced

fentanyl sparing effect without any adverse effects. This opioid sparing effect of pregabalin is because of alpha 2 delta receptor blockade induced reduction in release of several excitatory aminoacids. This blocks the central sensitisation process caused by the surgical incision induced activation of peripheral nociceptors. Hence, pregabalin produces an antihyperalgesic effect.

Pregabalin is a drug with good safety profile. It is not metabolised, do not interfere with microsomal p450 enzymes, and not protein bound. All these properties explain the lack of pharmacological drug interactions. Pregabalin acts on N-type calcium channels, whereas myocardium and other peripheral tissues have L-type calcium channels[6]. The lack of action on cardiac type calcium channels explains the absence of cardiovascular system related side effects. The commonest side effects of pregabalin are drowsiness and somnolence. Pregabalin lacks GABAnergic activity which explains the lack of retinal or optic nerve toxicity.[7]

Pregabalin has got the novel mechanism of action on alpha 2 delta subunit of neuronal calcium channels which helps in blunting the release of excitatory neuro aminoacids. Although the exact mechanism of attenuation of hemodynamic response to laryngoscopy and intubation by pregabalin is not known, this must be because of calcium channel blocking caused by pregabalin. Gabapentin reduced catecholamine

release from adrenal chromaffin cells.[33] Calcium channels are not completely blocked to the influx of calcium, but the calcium is not able to facilitate vesicular fusion.

In the method done, this study observed that premedication with 150mg pregabalin an hour before induction as a single dose attenuated hemodynamic response to laryngoscopy and tracheal intubation. It produced pre-operative sedation without prolonging the recovery from general anesthesia in patients undergoing abdominal surgery. Pre-operative pregabalin 150mg reduced patient controlled fentanyl requirement in the first 12hours after surgery.

SUMMARY

This prospective, randomised, double blinded, and placebo controlled study evaluated the efficacy of single oral dose of 150mg pregabalin given an hour before induction on attenuation of hemodynamic response to laryngoscopy and tracheal intubation.

Sixty ASA1 and 2 patients of 20 to 60 years age group of both sexes undergoing abdominal surgery were randomised into two groups

- Group-C – placebo
- Group-P – 150mg pregabalin

General anesthetic techniques were standardised. Sedation scale prior to induction was documented. Heart rate, systolic, diastolic, and mean blood pressure were recorded at baseline and at 1minute, 3minutes, and 5minutes after laryngoscopy and intubation. Duration of laryngoscopy, grading of laryngeal view, and time to recovery of response to simple oral commands were recorded. Post-operatively pain relief was provided through intravenous patient controlled fentanyl at a demand dose of 25mcg. Pain was assessed with numeric pain scale. Whenever the patient

gets pain score of more than 4, an additional dose of 25mcg of fentanyl was administered

Results were tabulated and statistical analysis was done using Microsoft excel, and SPSS software. Student t-test was used for quantitative variables and chi-square test for qualitative variables. With the patients matched for demographic profiles, the results showed that there was no significant difference in baseline hemodynamic variables between the two groups.

Pregabalin group patients remained sedated pre-operatively. There was significantly less elevation in blood pressure following laryngoscopy and intubation in pregabalin group. Although tachycardia occurred in both groups following intubation, the raise heart rate was significantly less in pregabalin group. There was no difference in recovery time.

Post-operative pain scores were comparable between the groups. Patients in pregabalin group required significantly less additional doses and total dose of patient controlled fentanyl over 12 hours after surgery.

There was no difference in the incidence of nausea and vomiting between the groups. None of the patients in both groups had bradycardia, hypotension, pruritis, or respiratory depression.

CONCLUSION

Premedication with 150mg of pregabalin an hour before induction causes significant attenuation of hemodynamic response to tracheal intubation and reduces post-operative fentanyl requirement without any side effects in patients undergoing abdominal surgery.

BIBLIOGRAPHY

1. Lowenstein E. Perianesthetic ischemic episodes cause myocardial infarction in humans - a hypothesis confirmed. Anesthesiology 1985; 62: 103-6.
2. Russell WJ, Morris RG, Frewin DB, Drew SE: Changes in plasma catecholamine concentrations during endotracheal intubation. Br J Anaesth 1981; 53:837–9
3. Rastogi B, Gupta K, Gupta PK, Agarwal S, Jain M, Chauhan H. Oral pregabalin premedication for attenuation of haemodynamic pressor response of airway instrumentation during general anaesthesia: A dose response study. Indian J Anaesth. 2012 Jan-Feb; 56(1): 49–54.
4. ANATOMY FOR ANAESTHETISTS, Harold Ellis, CBE, MA, DM, FRC, FACS, (Hon). ; p 17-37
5. Miller's Anaesthesia – 6th edition – Ronald D. Miller, p-1634
6. Gajraj NM. Pregabalin: its pharmacology and use in pain management. Anesth Analg 2007;105:1805–15
7. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004; 45: 13–8
8. Jeffrey A. Grass, MD, MMM. Patient-Controlled Analgesia. Anesth Analg 2005;101:S44 –S61

9. Miller’s Anaesthesia – 7th edition – Ronald D. Miller, p-2761
10. Reid LC, Brace DE. Irritation of the respiratory tract and its reflex effect upon heart. SurgGynaeObstet. 1940;70:157–62.
11. Burstein, C.L, lo Pinto, F.J., and Newman, W. (1950). Electrocardiographic studies during endotracheal intubation. Anesthesiology, 11, 224.
12. King BD, Harris LC, Greifenstein FE, Elder JD, Dripps RD. Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. Anesthesiology 1951;12:556-66.
13. Wycoff CC. Endotracheal intubation: effects on blood pressure and pulse rate. Anesthesiology 1960;21:153-8.
14. Prys-Roberts C, Greene L, Miloche R, Foex P: Studies of anaesthesia inrelation to hypertension. II. Haemodynamic consequences of induction andendotracheal intubation. Br J Anaesth 1984; 43:531–47
15. Shribman AJ, Smith G, Achola KJ: Cardiovascular and catecholamine responsesto laryngoscopy with and without tracheal intubation. Br J Anaesth 1987;59:295–9
16. Derbyshire DR, Chmielewski A, Fell D, Vater M, Achola K, Smith G: Plasma catecholamine responses to tracheal intubation. Br J Anaesth 1983; 55:855–60

17. Kovac AL. Controlling the hemodynamic response to laryngoscopy and endotracheal intubation. J Clin Anesth 1996; 8: 63–79
18. Low JM, Harvey JT, Prys-Roberts C, Dagnino J: Studies of anaesthesia in relation to hypertension. VII: Adrenergic responses to laryngoscopy. Br J Anaesth 1986;58:471-7.
19. John Bullington, MD, Stephanie M. Mouton Perry, MD, James Rigby, phD, The effect of advancing age on sympathetic response to laryngoscopy and tracheal intubation. Anesth Analg 1989; 68:603-8.
20. French JA, Kugler AR, Robbins JL, Knapp LE, Garofalo EA. Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures Neurology. 2003 May 27;60(10):1631-7.
21. Serhat KOC, Dilek Memis, Necdet Sut. The preoperative use of gabapentin, dexamethasone and their combination in vericocele surgery: A randomised controlled trial. Anesth Analg. 2007;105:1137–1142.
22. Fassoulaki A, Melemeni A, Paraskeva A, Petropoulos G: Gabapentin attenuates pressor response to direct laryngoscopy and tracheal intubation. Br J Anaesth 2006; 96:769 –73
23. Usha Bafna, Vipin K Goyal, and Ashish Garg A Comparison of Different Doses of Gabapentin to Attenuate the Haemodynamic

Response to Laryngoscopy and Tracheal Intubation in Normotensive Patients J Anaesthesiol Clin Pharmacol. 2011 Jan-Mar; 27(1): 43–46.

24. White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesth Analg. 2009 Apr;108(4):1140-5.
25. Sundar AS, Kodali R, Sulaiman S, Vakamudi M. The effects of preemptive pregabalin on attenuation of stress response to endotracheal intubation and opioid-sparing effect in patients undergoing off-pump coronary artery bypass grafting. Ann Card Anaesth 2012;15:18-25
26. Kumkum Gupta, Deepak Sharma, and Prashant K. Gupta Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: A comparative evaluation Saudi J Anaesth. 2011 Apr-Jun; 5(2): 179–184.
27. Mathiesen O, Jacobsen LS, Holm HE et al. Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. Br J Anaesth 2008; 101: 535–41
28. Jokela R, Ahonen J, Tallgren M, Haanpa¨a¨ M, Korttila K. Premedication with pregabalin 75 or 150 mg with ibuprofen to

control pain after day-case gynaecological laparoscopic surgery. Br J Anaesth 2008;100:834–40

29. Siun M. Burke, MB, and George D. Shorten, PhD Perioperative Pregabalin Improves Pain and Functional Outcomes 3 Months After Lumbar Discectomy. Anesth Analg 2010;110:1180–5.
30. P. W. H. Peng1, C. Li2, E. Farcas 1, A. Haley, W. Wong, J. Bender and F. Chung. Use of low-dose pregabalin in patients undergoing laparoscopic cholecystectomy. British Journal of Anaesthesia 105 (2): 155–61.
31. Stoelting RK. Circulatory changes during direct laryngosocpy and tracheal intubation- influence of duration of laryngoscopy with or without prior lidocaine. Anesthesiology. 1977; 47:381–4.
32. Hall AP, Thomson JP, Leslie NAP, Fox AJ, Kumar N, Rowbotham DJ. Comparison of different doses of remifentanil on the cardiovascular response to laryngoscopy and tracheal intubation. Br J Anaesth 2000; 84: 100–2
33. Robert D. Todd, M.D., Sarah M. McDavid, M.S., Rebecca L. Brindley, Ph.D., Gabapentin Inhibits Catecholamine Release from Adrenal Chromaffin Cells. Anesthesiology 2012; 116:1013–24

													GROUP							HEART RATE							SYSTOLIC BLOOD PRESSURE							DIASTOLIC BLLOD PRESSURE						
S.No	NAME	age	sex	WT	DNG	SUR	ASA	drug	D1	D2	RSS.1	HR-BL	HR-AP	HR-AI	HR-IL0	HR-IL1	HR-IL3	HR-IL5	SBP-BL	SBP-AP	SBP-AI	SBP-IL0	SBP-IL1	SBP-IL3	SBP-IL5	DBP-BL	DBP-AP	DBP-AI	DBP-IL0	DBP-IL1	DBP-IL3	DBP-IL5
1	saranraj	34	1	54	1	1	1	1	105		3	84	89	89	93	102	81	82	136	119	128	139	147	125	119	78	76	74	91	93	70	69
2	fathima	36	2	62	2	2	1	1	90		3	76	84	86	90	90	79	72	140	122	99	106	109	97	112	77	83	62	67	72	62	74
3	sumathi	40	2	58	2	2	1	1	85		4	68	74	72	81	83	71	72	117	103	95	114	122	135	136	83	67	66	81	83	96	94
4	mumtaz	35	2	54	1	1	2	1	115		3	70	82	84	88	88	77	73	110	110	107	117	121	94	93	76	74	77	90	91	65	66
5	palani	34	1	62	4	4	1	1	85		3	86	92	91	93	93	88	89	129	129	130	146	152	112	118	91	90	85	97	101	72	81
6	durai	27	1	60	3	3	1	1	75		3	78	82	80	86	88	76	78	124	114	101	142	148	107	109	80	74	68	103	107	74	76
7	nagendran	35	1	58	1	1	2	1	100		4	76	82	80	86	84	78	74	119	117	113	125	125	91	115	77	75	72	76	79	48	83
8	ellammal	34	2	56	3	3	1	1	70		3	76	86	84	89	92	80	76	114	112	100	148	156	110	101	75	76	65	99	108	81	67
9	saradha	45	2	60	5	5	1	1	110		4	86	92	94	108	112	96	88	123	122	111	159	164	159	133	86	86	75	104	107	102	93
10	manonmani	45	2	58	2	2	1	1	80		4	84	94	89	94	92	94	92	116	109	101	126	124	121	117	74	72	63	86	83	68	72
11	mary	42	2	64	2	2	2	1	90		2	76	81	84	89	93	86	88	132	132	127	138	136	112	114	80	82	76	94	96	79	76
12	lakshmi	36	2	64	6	6	2	1	100		2	70	76	79	86	88	77	74	122	116	99	126	126	101	103	82	74	68	93	94	79	78
13	anbazhagan	48	1	70	4	4	1	1	65		3	60	64	72	90	92	78	62	126	129	120	132	147	131	141	84	84	70	92	96	92	88
14	ghandhi	45	2	60	2	2	1	1	110		2	74	79	82	86	86	88	86	130	128	123	148	148	124	119	80	79	63	92	95	80	78
15	selvam	34	1	70	1	1	1	1	90		2	73	78	82	85	85	70	72	130	133	124	151	147	127	124	78	78	74	96	98	84	82
16	prema	41	2	64	6	6	1	1	80		3	74	80	86	90	92	74	76	124	121	118	127	134	110	112	78	76	74	86	89	71	74
17	arulmozhi	29	2	56	3	3	2	1	70		4	68	71	76	79	82	74	76	108	110	103	110	114	101	108	70	68	67	74	78	68	70
18	senthilkumar	32	1	80	1	1	1	1	105		2	76	74	78	80	80	75	76	110	110	108	114	119	102	101	76	72	72	65	78	73	68
19	mary	30	2	54	3	3	1	1	75		4	71	76	80	94	94	96	81	121	112	111	126	128	114	120	78	78	73	90	90	78	76
20	bhaskar	27	1	60	3	3	1	1	60		3	78	82	87	95	97	84	80	129	126	121	138	136	118	126	84	82	72	93	94	74	76
21	lakshmi	42	2	58	6	6	2	1	115		3	64	71	76	82	84	79	71	130	128	118	133	142	110	114	82	84	71	94	92	68	74
22	jothi	44	2	56	5	5	1	1	120		4	70	75	79	83	91	78	69	126	128	119	128	132	129	118	84	84	78	86	88	84	80
23	kannan	31	1	58	1	1	1	1	110		3	68	79	82	97	106	95	88	122	118	121	165	158	149	132	81	77	70	101	103	90	81
24	ravi	42	1	63	1	1	2	1	90		3	71	78	81	89	95	83	74	116	112	108	129	127	102	110	68	71	64	84	90	58	72
25	kalarani	37	2	57	5	5	1	1	115		4	80	88	82	96	103	90	75	112	116	102	108	107	117	121	71	74	61	67	69	73	72
26	venugopal	50	1	58	6	6	2	1	90		4	65	71	78	86	85	73	71	120	110	98	125	132	121	126	74	77	65	95	101	82	82
27	eswaran	43	1	58	2	2	1	1	100		3	82	79	86	107	113	99	87	132	129	120	159	167	148	136	81	82	76	102	105	92	84
28	selvi	40	2	60	5	5	2	1	120		3	71	77	80	84	87	87	73	113	117	100	123	128	116	118	69	71	65	84	84	72	76
29	pratheba	28	2	52	3	3	1	1	60		4	72	71	75	81	81	74	71	120	118	112	124	126	117	118	70	72	70	78	79	72	74
30	kalimuthu	50	1	50	4	4	2	1	90		3	69	73	78	85	85	76	73	112	114	110	108	112	114	120	70	74	65	70	72	80	84
31	sheela	29	2	76	1	1	1	2	100		2	72	83	84	88	95	88	82	116	116	120	139	142	118	116	68	76	77	99	101	82	76
32	saroja	38	2	58	1	1	1	2	90		2	72	80	82	90	91	82	76	140	132	142	133	134	119	109	86	80	87	74	78	67	72
33	manoharan	38	1	62	1	1	1	2	115		2	80	86	92	106	102	102	98	136	123	124	148	162	131	116	88	86	86	108	120	96	81
34	vasu	30	1	62	3	3	1	2	80		2	78	92	92	98	96	88	82	134	121	117	186	199	149	117	81	66	75	108	115	92	81
35	rajamalar	26	2	45	3	3	1	2	75		2	74	79	84	91	92	81	76	110	110	95	142	133	125	122	70	77	65	102	103	95	89
36	savithri	36	2	55	1	1	1	2	110		2	86	92	89	101	108	92	80	126	122	119	158	162	135	126	80	88	77	113	116	98	86
37	nareshkumar	21	1	56	3	3	1	2	56		2	71	74	79	89	88	72	74	120	118	116	121	128	112	116	78	71	76	82	86	71	70
38	vasanthi	40	2	52	5	5	2	2	95		2	70	74	79	89	94	71	76	124	122	116	139	142	128	118	82	82	74	89	98	84	78
39	shakila	39	2	63	5	5	2	2	110		2	76	78	82	86	88	86	82	110	99	90	101	102	101	92	71	62	54	68	69	66	63
40	padmavathi	26	2	55	1	1	1	2	120		2	76	78	74	96	94	86	92	124	117	112	139	144	124	152	83	69	70	82	80	78	113
41	chinapillai	47	2	42	2	2	2	2	105		2	78	82	74	104	102	108	107	116	123	102	152	147	124	102	73	79	80	94	98	88	72
42	pothammal	45	2	60	6	6	1	2	90		2	76	84	86	102	98	88	80	141	139	139	162	165	152	132	88	90	89	106	107	100	92
43	manikandan	41	1	74	4	4	1	2	75		2	71	75	79	84	82	86	80	126	128	122	187	190	146	138	82	81	80	132	123	85	82
44	karthik	22	1	54	3	3	1	2	70		2	76	82	86	108	112	92	81	109	112	110	153	160	136	125	78	78	74	125	122	92	91
45	devamani	40	2	72	2	2	2	2	95		2	81	86	86	92	92	84	81	132	130	118	149	157	142	136	80	81	76	98	95	84	78
46	anusuya	22	2	57	3	3	1	2	90		2	69	73	78	88	86	75	71	112	113	108	142	139	118	110	70	70	62	86	92	76	74
47	gopal	40	1	55	2	2	1	2	85		2	70	76	79	106	110	95	88	126	121	120	163	165	142	131	84	82	78	100	104	86	80
48	radha	41	2	58	2	2	1	2	96		2	73	71	83	89	95	87	70	112	114	108	133	138	117	112	70	68	71	84	86	69	70
49	mekala	35	2	65	6	6	2	2	100		2	79	85	86	99	99	82	74	120	121	112	162	171	141	118	70	70	62	109	108	87	79
50	amudha	21	2	54	3	3	1	2	70		2	68	74	75	89	92	84	76	106	111	102	105	109	111	118	71	69	65	79	80	77	81
51	shanthi	39	2	48	2	2	2	2	80		2	76	82	86	90	96	85	71	132	129	99	157	163	131	141	78	74	63	99	102	87	90
52	arumugam	41	1	56	4	4	2	2	75		2	82	84	81	105	109	98	87	140	118	110	152	165	111	121	82	71	69	94	92	74	78
53	rajan	36	1	60	2	2	1	2	90		2	75	79	78	99	110	92	86	142	138	127	171	169	158	131	84	84	80	105	106	92	87
54	rafiq	27	1	81	1	1	1	2	95		2	71	75	80	112	112	98	89	118	118	116	159	167	139	127	72	71	72	110	111	94	86
55	kumaran	42	1	62	6	6	2	2	100		2	78	84	88	96	101	89	77	128	126	130	148	151	119	121	82	82	76	93	96	78	83
56	prabakaran	28	1	70	4	4	1	2	85		2	70	73	73	90	93	88	72	112	114	109	132	131	111	112	71	72	68	89	90	73	78
57	deepa	21	2	56	3	3	1	2	70		2	71	78	79	88	87	76	74	110	112	108	138	138	119	116	71	70	69	86	89	78	72
58	vasantha	40	2	52	5	5	2	2	110		2	70	74	75	83	84	76	77	120	122	116	123	126	108	112	72	70	68	82	82	71	76
59	santhosam	48	2	46	2	2	2	2	90		2	78	84	88	96	97	88	81	126	118	121	159	167	151	137	78	76	72	101	105	98	86
60	velu	42	1	64	6	6	1	2	80		2	80	86	84	101	101	94	86	130	129	126	172	175	156	143	82	82	71	113	113	98	86

MEAN BLOOD PRESSURE							VISUAL ANALOG SCALE - REST						VISUAL ANALOG SCALE - MOVEMENT						RAMSAY SEDATION SCALE						COMPLICATIONS					FENTANYL REQUIREMENT		LD
MBP-BL	MBP-AP	MBP-AI	MBP-IL0	MBP-IL1	MBP-IL3	MBP-IL5	VR-0	VR-1	VR-2	VR-4	VR-8	VR-12	VM-0	VM-1	VM-2	VM-4	VM-8	VM-12	R-0	R-1	R-2	R-4	R-8	R-12	PONV	HYPO	BRADY	RES.DEP	PRU	T.DMND	T.DOSE	AD.DOSE	RT	
97	90	92	107	111	88	85	8	3	3	2	2	2	10	8	6	3	2	2	2	3	3	3	2	2	0	0	0	0	0	7	200	0	10	12
98	96	74	80	84	73	86	6	2	2	3	2	2	6	4	4	4	3	3	3	4	4	3	3	2	1	0	0	0	0	7	198	0	8	14
94	79	75	92	96	109	108	4	2	2	3	3	2	8	4	4	6	4	4	3	4	4	2	3	2	0	0	0	0	0	5	150	0	8	10
87	86	87	99	101	75	75	6	3	3	2	2	2	7	6	4	4	3	3	4	4	3	2	2	3	0	0	0	0	0	6	175	0	12	14
102	102	96	113	116	81	89	6	4	3	3	2	2	8	6	4	4	3	3	2	4	4	2	3	3	0	0	0	0	0	8	225	0	10	12
94	87	79	116	121	85	87	4	3	2	2	3	2	6	4	4	5	4	4	3	3	3	2	2	2	0	0	0	0	0	6	175	0	12	11
91	89	85	92	94	60	90	7	2	2	3	3	2	8	4	3	3	3	4	3	4	4	4	3	2	1	0	0	0	0	8	223	0	14	12
88	88	77	115	124	91	78	6	2	2	4	2	2	7	4	4	8	4	4	3	3	3	2	2	2	1	0	0	0	0	6	175	0	11	12
98	98	87	122	126	121	106	8	4	2	6	2	2	10	6	3	6	3	3	2	3	3	2	3	3	0	0	0	0	0	6	198	1	8	10
88	84	75	99	96	82	82	6	8	3	2	2	2	8	8	6	4	4	3	2	2	2	3	3	2	0	0	0	0	0	7	223	1	10	12
97	98	93	108	109	90	88	6	2	2	4	2	2	8	4	3	3	4	3	3	4	4	4	3	3	0	0	0	0	0	5	150	0	10	15
95	88	78	105	104	86	86	8	4	2	2	4	2	8	6	4	4	6	3	2	3	3	3	2	2	0	0	0	0	0	8	225	0	12	10
98	99	86	105	113	105	105	6	2	2	2	2	2	8	4	4	4	4	4	2	2	3	3	2	2	0	0	0	0	0	5	150	0	11	12
96	95	83	110	112	95	92	6	2	2	2	6	2	8	4	4	4	6	4	3	3	3	2	2	3	1	0	0	0	0	6	200	1	10	11
95	96	90	114	114	98	96	8	4	3	3	4	2	8	6	4	4	6	3	2	2	3	3	2	2	0	0	0	0	0	9	250	0	8	12
93	91	88	99	104	84	86	6	3	2	3	2	2	7	4	4	3	3	3	3	4	4	4	3	2	1	0	0	0	0	5	150	0	8	14
82	82	79	86	90	79	82	4	2	2	4	3	3	6	4	3	4	3	3	3	4	4	3	2	2	1	0	0	0	0	5	150	0	10	10
87	84	84	81	91	82	79	8	4	3	3	3	3	8	6	6	4	4	4	2	3	3	2	2	3	0	0	0	0	0	10	275	0	12	12
92	89	85	102	102	90	90	6	3	3	3	4	3	8	4	6	4	4	4	3	4	4	4	2	3	0	0	0	0	0	6	175	0	10	12
99	96	88	108	108	88	92	8	5	3	3	4	2	8	8	4	4	5	4	2	3	3	2	2	3	1	0	0	0	0	9	250	0	8	14
98	98	86	107	108	82	87	6	3	3	3	4	3	6	4	4	5	5	4	3	4	4	3	2	2	1	0	0	0	0	11	300	0	8	10
98	98	91	100	102	99	92	6	3	4	3	3	3	8	4	4	5	4	4	4	4	4	3	3	2	1	0	0	0	0	7	200	0	13	12
94	90	87	122	121	109	98	7	4	3	3	3	3	8	5	4	4	4	4	3	3	3	2	2	3	0	0	0	0	0	10	275	0	12	13
84	84	78	99	102	72	84	6	3	3	5	3	2	6	4	4	7	4	3	3	3	3	3	2	2	1	0	0	0	0	11	325	1	11	12
84	88	74	80	81	87	88	6	2	2	4	3	3	8	4	4	3	3	3	4	4	3	3	3	2	0	0	0	0	0	6	175	0	10	10
89	88	76	105	111	95	96	7	3	3	2	2	3	7	5	4	4	4	3	4	4	4	2	3	2	1	0	0	0	0	6	175	0	8	12
98	97	90	121	125	110	101	8	4	2	2	3	2	8	6	3	3	4	3	3	3	4	4	2	2	0	0	0	0	0	10	275	0	8	10
83	86	76	97	98	86	90	6	3	3	2	2	3	6	4	3	3	4	3	3	4	4	3	2	2	0	0	0	0	0	6	175	0	9	14
86	87	84	93	94	87	88	6	2	2	2	3	2	6	3	4	4	3	3	4	4	3	3	2	2	0	0	0	0	0	5	150	0	10	12
84	87	80	82	85	91	96	8	4	4	2	3	3	8	6	4	4	4	3	3	3	4	4	2	2	0	0	0	0	0	6	175	0	12	14
84	89	91	112	114	94	89	6	4	3	3	3	3	8	6	4	4	4	4	2	2	3	3	3	2	0	0	0	0	0	12	325	0	14	10
104	97	107	93	96	78	81	8	6	3	3	5	3	8	8	4	4	6	4	2	2	2	3	3	2	1	0	0	0	0	15	425	1	10	11
104	98	98	121	134	107	92	6	8	3	4	3	3	8	8	6	4	4	3	2	2	3	3	2	2	0	0	0	0	0	13	375	2	11	10
98	77	86	134	164	111	91	8	3	3	3	4	2	8	6	4	4	6	3	2	2	2	3	2	3	1	0	0	0	0	14	373	0	8	10
83	84	72	115	111	103	99	7	3	3	6	3	3	8	8	4	6	4	4	2	2	2	3	2	2	0	0	0	0	0	11	325	1	8	14
95	97	89	128	131	109	97	6	4	2	2	4	2	10	6	3	3	4	3	2	2	2	2	3	3	1	0	0	0	0	14	398	1	13	12
92	86	89	95	100	84	85	4	2	2	2	6	3	6	3	3	3	6	4	2	2	2	2	2	2	1	0	0	0	0	13	348	0	11	12
96	95	88	105	112	98	91	5	3	3	3	4	3	7	6	6	4	4	3	2	2	3	3	2	2	0	0	0	0	0	10	275	0	8	10
84	74	66	79	80	78	73	6	4	2	3	3	3	8	6	4	4	3	3	2	2	3	2	2	2	1	0	0	0	0	8	248	1	8	12
96	85	84	101	101	93	126	6	3	3	6	3	3	8	6	4	8	4	4	1	2	2	1	2	2	1	0	0	0	0	13	375	1	10	14
87	93	87	113	114	100	82	5	2	2	3	3	2	7	4	3	4	4	5	1	2	2	3	2	2	1	0	0	0	0	10	275	0	11	15
106	106	106	125	126	117	105	7	3	3	4	3	3	8	6	4	4	3	3	2	2	2	2	3	2	0	0	0	0	0	12	325	0	14	10
96	96	94	150	145	105	100	6	4	3	4	3	3	8	6	4	5	4	4	2	2	3	3	2	2	0	0	0	0	0	13	348	0	12	10
88	89	86	134	134	106	102	7	4	3	3	2	2	8	7	5	4	4	3	1	2	2	3	2	3	0	0	0	0	0	10	275	0	11	12
97	97	90	115	115	103	97	8	4	2	3	3	4	8	6	4	5	4	4	1	2	2	3	3	2	1	0	0	0	0	12	323	0	14	10
84	84	77	104	107	90	86	6	3	3	2	3	2	8	4	4	4	3	3	2	2	3	3	2	2	0	0	0	0	0	9	250	0	10	10
98	95	92	121	124	104	97	7	4	3	3	3	3	7	5	4	4	4	3	2	2	2	3	2	2	0	0	0	0	0	12	325	0	8	11
84	83	83	100	103	85	84	8	3	3	4	2	2	8	5	4	4	4	3	2	2	2	3	3	2	0	0	0	0	0	8	250	1	8	10
86	87	78	126	129	105	92	8	4	4	5	3	3	8	7	4	4	5	4	1	2	2	3	3	2	0	0	0	0	0	12	350	1	8	10
82	83	77	87	89	88	93	6	2	2	3	3	3	6	4	4	5	4	3	2	3	3	2	2	2	0	0	0	0	0	6	175	0	10	12
96	92	75	118	122	101	107	8	5	3	3	2	2	8	8	4	5	4	3	1	2	2	2	3	3	1	0	0	0	0	10	300	1	10	12
101	86	82	114	116	86	92	7	4	4	3	3	3	7	5	4	4	4	4	2	2	2	3	2	2	0	0	0	0	0	12	325	0	8	14
103	102	95	127	127	114	101	8	5	3	3	5	3	8	6	4	4	6	4	1	2	2	2	3	3	0	0	0	0	0	13	375	1	11	12
87	86	86	126	129	109	99	6	3	3	8	4	3	6	6	4	8	5	4	1	2	2	2	2	2	0	0	0	0	0	14	375	0	12	10
97	96	94	111	114	91	95	7	4	3	3	2	2	7	5	4	4	4	4	2	2	2	3	3	2	1	0	0	0	0	11	325	1	8	10
84	86	81	103	103	85	89	6	3	3	3	4	3	8	6	4	4	4	3	2	2	2	3	2	2	0	0	0	0	0	10	275	0	10	12
84	84	82	103	105	91	86	6	4	3	3	3	2	7	5	4	3	3	3	2	2	3	3	2	2	0	0	0	0	0	8	225	0	8	14
88	87	84	95	96	83	88	7	4	4	3	3	3	8	6	4	4	4	3	2	3	3	3	2	2	0	0	0	0	0	9	275	1	11	11
94	90	88	120	125	115	103	8	4	3	3	3	2	8	6	4	4	4	3	2	2	2	2	3	3	0	0	0	0	0	10	300	1	10	12
98	97	89	132	133	117	105	7	4	3	3	5	3	8	6	4	4	6	4	1	2	2	2	2	3	1	0	0	0	0	13	375	1	8	10

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. P. Ramesh Kumar
PG in MD Anaesthesia
Madras Medical College, Chennai -3

Dear Dr. P. Ramesh Kumar

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Evaluation of oral pregabalin premedication on attenuation of hemodynamic response to laryngoscopy and as adjuvant in acute pain management in normotensive patients" No.03092012.

The following members of Ethics Committee were present in the meeting held on 13.09.2012 conducted at Madras Medical College, Chennai -3.

1. Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2. Prof. Pregna B. Dolia MD Vice Principal, Madras Medical College, Chennai -3 Director , Institute of Biochemistry, MMC, Ch-3	-- Member Secretary
3. Prof. B. Vasanthi MD Professor of Pharmacology ,MMC, Ch-3	-- Member
4. Prof. M. Reghu MD Director, Inst. Of Internal Medicine, MMC, Ch-3	-- Member
5. Prof. MD. Ali. MD.DM Prof & HOD of MGE, MMC, Ch-3	-- Member
6. Prof. P. Karkuzhali. MD Director i/c, Prof., Inst. of Pathology, MMC, Ch-3	-- Member
7. Prof. Bavani Shankar. MS Prof of General Surgery, MMC, Ch-3	-- Member
8. Thiru. S. Govindsamy. BABL	-- Lawyer
9. Tmt. Arnold Soulina MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

INTRODUCTION

The act of laryngoscopy and intubation elicits reflex tachycardia and hypertension. Though this stress response is transient, it is profound enough to cause undesired effects on cardiovascular system like dysrhythmias, and myocardial ischemia. Hence, this laryngoscopy and intubation induced stress response needs to be attenuated.

The reflex response to instrumentation of airway is sympathetic rather than a vasovagal response. The previous studies which showed increase in serum catecholamine level during laryngoscopy and intubation supports the fact that the reflex response is sympathetic. Blunting of the stress response by beta receptor blockade, further confirms this concept.

PREMEDICATION WITH ORAL PREGABALIN ON ATTENUATION OF HEMODYNAMIC PRESSOR RESPONSE TO LARYNGOSCOPY AND INTUBATION

NAME: AGE/SEX: DATE:

UNIT: IP NO': WARD:

DIAGNOSIS: PROCEDURE:

ASA- GROUP: BODY WEIGHT:

PRE-OPERATIVE:

1.Comorbid illness - 2.Medications - 3.Airway

PRE-MEDICATIONS:	DOSE	ROUTE	DATE/TIME
1.Tab.Ranitidine	150mg	p/o	
2.Tab.Alprazolam	0.5mg	p/o	
3.			

INTRA-OPERATIVE PERIOD:

Midazolam- Glycopyrrolate- Fentanyl-

Thiopentone- Succinylcholine-

LARYNGOSCOPY: C.L- DURATION-

Maintenance-

Total fentanyl- Total atracurium-

Reversal- Extubated

Duration of procedure - Duration of anesthesia -

Delayed recovery - PONV- Shivering-

HEMODYNAMIC PARAMETERS:

	RSS	HR	SBP	DBP	MAP	SPO2
BASELINE						
AFTER PREMEDICATION	_					
AFTER INDUCTION	_					

AFTER LARYNGOSCOPY AND INTUBATION:

	HR	SBP	DBP	MAP	SPO2
IMMEDIATELY (0 MIN)					
1 MIN					
3 MIN					
5 MIN					

PACU OBSERVATION: Admission- Discharge- Stay-

PCA:Started- Concluded- Duration-

Drug- Concentration- **10 mcg/ml** Loading-

Demand- Lockout- Infusion- **Nil**

Additional dose-

	RSS	VAS		HR	RR	BP	SPO2	Additional dose
		Rest	Movement					

Total demands- good ones- Total dosage-

ADVERSE EFFECTS**:**

Events	Treatment	Remarks

PATIENT CONSENT FORM

Study title : EVALUATION OF ORAL PREGABALIN PREMEDICATION ON ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND AS ADJUVANT IN ACUTE PAIN MANAGEMENT IN NORMOTENSIVE PATIENTS

Study centre : Institute of Anaesthesiology and Critical Care,

Rajiv Gandhi Memorial Govt General Hospital, Chennai.

Participant name : Age: Sex: I.P.No:

I confirm that i have understood the purpose of procedure for the above study. i have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the pitfall in the procedure. I have been explained about the safety, advantage and disadvantage of the technique.

I understand that my participation in the study is voluntary and that i am free to withdraw at anytime without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to current study and any further research that may be conducted in relation to it, even if i withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

Time:

Date: signature / thumb impression of patient

Place: patient name:

Signature of the investigator:

Name of the investigator: